Case

Sonika Puri
Case Presentation

ESRD; on Hemodialysis since 07/2011

60 yo. AA male with h/o HIV/AIDS (Cd 4 count-89/ml, VL-undetectable) – Whether he is a candidate for Renal Transplant ?

--Etiology of ESRD : chronic kidney disease since 1999-2000, egfr 50-60ml/min/1.73m2, bland urinary sediment, nephrotic range proteinuria -5-7gm in 2003-2005

-- gradually progressive since then in the setting of a low cd4 count (80-190/ml) though mostly undetectable viral load. Other work up negative d/d : HIVAN/ focal sclerosis / amyloidosis

PMH
--Diagnosed with HIV in 2002, sec. to unprotected sexual contact. Cd 4-31/ml with high viral load
--He has been on HAART since then with good compliance. No opportunistic infections
--CAD s/p cath in 2001- diffuse disease, medical management
--systolic heart failure: ef 40%
PMH continued:
-h/o afib, rate controlled and anticoagulation
-Long standing h/o htn
- gout

Allergy: none

Meds:
Allopurinol
Losartan
Coreg
Darunavir
Lamivudine
Pravastatin
Bactrim m/w/f
Tenofovir
Warfarin
Ritonavir
Phoslo
- Family history:
  Hypertension in parents, no known kidney disease

Social: prior h/o smoking, quit several years back, no etoh or illicit drug use

ROS: neg other than occasional mild abd discomfort

o/e bp 128/70  pr 60

Gen: middle aged AA male
Heent: mild palor, no icterus
Chest: bl clear
Cvs: 2/6 systolic mur, s2, rrr
Abd: soft, nt, + hepatomegaly, no splenomegaly
Extr: warm, no edema, lue fistula with good thrill and bruit.
<table>
<thead>
<tr>
<th>Lab</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hep B s ab</td>
<td>Positive</td>
</tr>
<tr>
<td>Hep B s ag n</td>
<td>neg</td>
</tr>
<tr>
<td>Hep C a b</td>
<td>Neg</td>
</tr>
<tr>
<td>Syphilis serologies</td>
<td>Neg</td>
</tr>
<tr>
<td>Serum electrophoresis/ IF</td>
<td>No monoclonal band</td>
</tr>
<tr>
<td>Hba1c</td>
<td>5.0-5.7</td>
</tr>
</tbody>
</table>

Echo: Moderately reduced systolic function, ef 40%, normal RV function. Dilated La

Abd usg: hepatomegaly 18cm, no splenomegaly

Lipid profile: TG 181 (151-322 mg/dl)
HDL : 31 (34-48mg/dl)
LDL: 108 (65-131mg/dl)
**HIV AND CKD**

- Etiologies for kidney disease in HIV
  - HIVAN (10% of patients with HIV)
  - Immune mediated Glomerulonephritis
  - TMA
  - Drug-induced renal failure

- Exact prevalence of HIV infection in dialysis units is variable - 0.4%-1.5%; Brazil -----14%     Europe ------0-5%

- Third leading cause of ESRD in AA after DM/ ??HTN

*Trullas et al, KI 2011;  Frasetto et al, Nat.Rev.Neph 2009*
Figure 2. Prevalent cases of ESRD with HIV/AIDS, 1995 to 2000.

Figure 3. Percentage of total prevalent ESRD patients with HIV/AIDS, 1995 to 2000.
### HIV and CKD

**Mean CD4 count:** 328/305 (C/AA)  
*Choi et al, KI 2007*

#### Table 1: Demographic and clinical characteristics of the cohort at baseline

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total cohort n (percent)</th>
<th>HIV n (percent)</th>
<th>Diabetes n (percent)</th>
<th>No HIV or diabetes n (percent)</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)*</td>
<td>202,927 (100.0)</td>
<td>534 (0.3)</td>
<td>88,340 (43.5)</td>
<td>114,223 (56.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>180,638 (89.0)</td>
<td>265 (49.6)</td>
<td>76,765 (86.9)</td>
<td>103,692 (90.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Black</td>
<td>22,289 (11.0)</td>
<td>269 (50.4)</td>
<td>11,575 (13.1)</td>
<td>10,714 (9.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>196,600 (96.9)</td>
<td>529 (99.1)</td>
<td>86,195 (97.6)</td>
<td>110,003 (96.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Female</td>
<td>6,327 (3.1)</td>
<td>5 (0.9)</td>
<td>2,145 (2.4)</td>
<td>4,182 (3.7)</td>
<td></td>
</tr>
<tr>
<td>CKD (eGFR)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>45-59</td>
<td>120,587 (59.4)</td>
<td>298 (55.8)</td>
<td>48,152 (54.5)</td>
<td>72,226 (63.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>30-44</td>
<td>61,594 (30.4)</td>
<td>140 (26.2)</td>
<td>28,597 (32.4)</td>
<td>32,903 (28.8)</td>
<td></td>
</tr>
<tr>
<td>15-29</td>
<td>17,838 (8.8)</td>
<td>67 (12.6)</td>
<td>9,908 (11.2)</td>
<td>7,889 (6.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>&lt;15</td>
<td>2,908 (1.4)</td>
<td>29 (5.4)</td>
<td>1,683 (1.9)</td>
<td>1,205 (1.1)</td>
<td></td>
</tr>
<tr>
<td>Serum creatinine (mg/dl)</td>
<td></td>
<td>1.75 ± 0.76</td>
<td>2.31 ± 0.63</td>
<td>1.83 ± 0.82</td>
<td>1.69 ± 0.69</td>
</tr>
<tr>
<td>Comorbidities</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV</td>
<td>534 (0.3)</td>
<td></td>
<td>170 (31.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DM</td>
<td>88,340 (43.5)</td>
<td></td>
<td></td>
<td>100,156 (87.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HTN</td>
<td>183,959 (90.7)</td>
<td></td>
<td>367 (68.7)</td>
<td>100,156 (87.7)</td>
<td>&lt;0.001</td>
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<tr>
<td>CAD</td>
<td>123,657 (60.9)</td>
<td></td>
<td>136 (25.5)</td>
<td>63,809 (55.9)</td>
<td>&lt;0.001</td>
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<tr>
<td>CHF</td>
<td>70,733 (34.9)</td>
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<td>93 (17.4)</td>
<td>32,802 (28.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CVA</td>
<td>57,199 (28.2)</td>
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<td>62 (11.6)</td>
<td>28,907 (25.3)</td>
<td>&lt;0.001</td>
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<tr>
<td>PVD</td>
<td>61,370 (30.2)</td>
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<td>67 (12.6)</td>
<td>28,976 (25.4)</td>
<td>&lt;0.001</td>
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<tr>
<td>COPD</td>
<td>79,317 (39.1)</td>
<td></td>
<td>153 (28.7)</td>
<td>44,574 (39.0)</td>
<td>&lt;0.001</td>
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<tr>
<td>HCV</td>
<td>2423 (1.2)</td>
<td></td>
<td>146 (27.3)</td>
<td>1182 (1.3)</td>
<td></td>
</tr>
</tbody>
</table>

*Choi et al, KI 2007*
- Survival rate at 1, 3, and 5 years for HIV-infected patients on dialysis of 95.2%, 71.7% and 62.7% respectively.
- These were significantly lower than those of a matched HIV-negative cohort of dialysis patients.
HIV and Renal Transplantation

- Selection of the right patient population for transplantation
- Risk of opportunistic infections and progression of HIV in the setting of increased immunosuppression
- Increased risk of malignancies in the setting of immunosuppression.
- Drug Interactions

**QUESTION** n= 148 centres, Resp rate 60%

<table>
<thead>
<tr>
<th></th>
<th>YES (%)</th>
<th>NO (%)</th>
</tr>
</thead>
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<tr>
<td>Consideration for CRT in a HIV-infected ESRD pt.</td>
<td>9</td>
<td>88</td>
</tr>
<tr>
<td>Consideration for LKT in a HIV-infected ESRD pt.</td>
<td>5</td>
<td>91</td>
</tr>
</tbody>
</table>

Aaron et al Transplantation 1998
- Mean fup of 2.9 yrs in Non-hiv and 2.6yrs in HIV cohort

- At baseline – similar in terms of sex, DM, HCV co-infection, rate of rejection (18%), dialysis within one week of tx.

- ~40% used induction antibody use.
- 40% Tacro, 60% Csa, MMf 75%-80%
- Lower representation of AA population in the HIV positive group
HIV and Transplantation

- Earliest pilot study by Stock et al. (UCSF) – 14 pts (10 kidney, 4 liver transplants)

- Standard selection criteria for renal transplantation PLUS

- HIV-positive, stable ART regimen x 3 months, undetectable viral count, CD4 > 200/ml for renal transplant recipients and >100/ml for liver recipients.

- No history of opportunistic infections or neoplasms

- Antibody induction therapy was not used. Maintenance IS was cyclosporine (150-200ng/ml), MMF 2-3gm, steroids

*Transplantation, 2003*
- 100% patient and graft survival, rate of rejection – 50%
- 3/5 patients treated with Thymoglobulin for type 2 vascular rejection
- Treatment with Thymo led to suppression of Cd4 count < 100/ml with prolonged recovery time- Staph. aur endocarditis, Pseudomonas sepsis
- Viral counts remained suppressed.
- 9 patients had abnormal anal cytology/histology at baseline with 75% - Anal HPV positive
- All progressed to higher grade AIN. ALL pts who were negative for HPV turned positive.
-Prospective, non-randomized trial –HIV type 1, CD4 cells >200/ml (mean count- 524), undetectable viral count (< 50 copies/ml), stable on HAART for >16 weeks.

-Previously treated opportunistic infections: except
  --- visceral KS, PML, primary CNS lymphomas, chronic intestinal cryptosporidiosis

-2003-2009, 150 patients

Donor –median age: 41 yrs

Recipient- median age: 46 yrs
  -males :78%  -AA : 69%
  -25% HIVAN
  -9% : DM
  -20% : co-infection with HCV
Prophylaxis
- Lifelong therapy for PCP
- Fluconazole for fungal infections, valgancyclovir for CMV infections
- Macrolides for MAC prophylaxis for Cd4 <75/ml
- Secondary prophylaxis for prior opportunistic infections for one month after tx or rejection treatment.

- Additionally, pt’s with HCV co-infection required a liver biopsy showing no e/o cirrhosis, if Hep B positive- negative HepB sagn.
- 11 pts died - 3 cv causes, 2-sepsis

- 13 graft failure: 5 chronic allograft nephropathy, 3-vascular thrombosis, 3- rejection

- Delayed Graft function: 15% with LDK, 46% with CRT

- Graft loss: HR 2.5 (CI 1.1-5.6, P<0.03) use of ATG, use of LDT-protective
HCV - vs. HCV + PATIENTS
Patient and Graft survival: 1 year 96.1%/ 90.9% vs. 88.3%/88.6% resp. (NS)
-similar rate of rejection

Rejections: 33% rejection rate in 1st year, 63% ACR, 10% mixed
-MVA: use of DDK, Csa as IS
-48% steroid responsive
-pts with rejection had significantly lower egfr at 1yr 51.8ml/min/vs 60.5 ml/min
P <0.05, at 3yrs– 34% vs 64% (p<0.05)

HIV AND OS:
2 new cases of KS, 1 case of candida esophagitis, presumed pcp and cryptosporidiosis, 1 case of hivan in a Cauc. Male/cauc.LDK, high Cd4 count, 2nd case Aamale/ AA DDK, with low Cd4 count

ATG: significant drop in Cd4 count (-238/vs. -135) from baseline to 1yr
32% patients had detectable viral load, ~90% detectable only once.

Infections: 38% : 69% bacterial , 60% within 6months- higher in pts with ATG(x2) / HCV positive

9 neoplasms : 2 KS, 2 RCC, 2 Oral Squamous-cell cancers , skin BCC
IMMUNOSUPPRESSION

- MMF has virostatic effect from the depletion of guanosine nucleosides required for viral cycle.
- CSA and tacrolimus have well documented selective inhibition of infected cell growth.
- Sirolimus - some anti-retroviral activity; decreases the expression of CCR5 on monocytes/lymphocytes thereby potentially reducing HIV entry into these cells.
- Sirolimus can be used as an alternative to CNI (however cannot be used for eGFR < 40 ml/min; monitored for proteinuria.
IMMUNOSUPPRESSION

- **METABOLIC SIDE EFFECTS**: hyperlipidemia with CNI/sirolimus/protease inhibitors
- Induction with IL-2 inhibitors is recommended, routine use of ATG is not recommended

Renal transplantation in patients with HIV

*Frasetto, Stock: Nat.Rev. Nephrology 2009*
DRUG INTERACTIONS

Protease inhibitors can markedly increase levels of Csa/Tacro and sirolimus – inhibition of CYP 3A4, hence LOWER DOSES are required.

--similarly discontinuing Pis can precipitate acute rejection

-NNRTIs –induce CYP 3A4, hence higher doses of Csa/tacro may be required.

-No clinically significant interaction with MMF has been noted.

Trullas et al, KI 2010
# Opportunistic Infections

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## Table 1: Recommended Prophylaxis Regimens for Renal Transplantation Candidates with HIV

<table>
<thead>
<tr>
<th>Condition</th>
<th>Primary Prophylaxis*</th>
<th>Secondary Prophylaxis†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumocystis carinii pneumonia</td>
<td>Indicated for life; to be initiated immediately upon inclusion in transplantation list. Preferred treatment: trimethoprim–sulfamethoxazole. Alternatives: ursodeoxycholic acid or dapsone—if not glucose-6-phosphate dehydrogenase-deficient—or atovaquone.</td>
<td>Same as for primary prophylaxis</td>
</tr>
</tbody>
</table>

*No history of infection. Additional alternatives, drug interactions and dosing in renal insufficiency are available elsewhere. †Prior history of the infection. Additional alternatives, drug interactions and dosing in renal insufficiency are available elsewhere. ‡Secondary prophylaxis should also be reinstated immediately post-transplantation for 1 month and during the treatment of acute rejection for 1 month following completion of the rejection therapy. If CD4+ T-cell count is suppressed, continuation should be guided by the CD4+ T-cell count.
Screening for cervical cancers and anal cancers as is done for HIV positive patients.

Higher risk of Hepatocellular cancer in patients with HBC/HCV co-infection - routine surveillance

Screening for skin cancers
**Box 1 | Proposed selection criteria for renal transplantation in HIV-1 infection**

**Exclusion criteria**
- Age <1 year
- Detectable HIV-1 RNA
- History of progressive multifocal leuкоencephalopathy, chronic intestinal cryptosporidiosis of at least 1 month duration, lymphoma (Burkitt, immunoblastic or brain)
- History of multidrug-resistant fungal infection (e.g. resistant Candida krusei or Candida glabrata infection) not expected to respond to available oral antifungal agents
- History of any neoplasms except those specified in the inclusion criteria below
- Substance use as per local transplantation policy
- Advanced cardiac or pulmonary disease as per local transplantation policy
- Anatomic abnormalities precluding transplantation
- Use of interleukin 2 or granulocyte-macrophage colony-stimulating factor in the 6 months before transplantation
- Cirrhosis on liver biopsy in patients with hepatitis C co-infection, unless candidate is being listed for combined liver and kidney transplant
- Substantial wasting and/or malnutrition
- Concomitant conditions that, in the judgment of care providers, preclude transplantation or immunosuppression

**Inclusion criteria**
- Meeting standard criteria for inclusion in renal transplantation list
- CD4+ T-cell count ≥200/ml at any time in the 16 weeks before transplantation
- No change in antiretroviral regimen for 3 months before transplantation
- Primary medical care provider has expertise in HIV treatment
- Ability and willingness to comply with immunosuppression protocol and antiretroviral therapy
- Ability and willingness to undergo prophylaxis for pneumocystis pneumonia, herpes virus and fungal infection
- If hepatitis C co-infection is present, ability and willingness to undergo frequent post-transplantation monitoring including hepatitis C treatment as mandated by medical care provider and collection of liver biopsy samples
- If a history of pulmonary coccidioidomycosis exists, patient must be disease-free for at least 5 years before transplantation
- If a history of neoplasms such as cutaneous Kaposi sarcoma, in situ anogenital carcinoma, adequately treated basal or squamous cell carcinoma of the skin or solid tumors treated with curative therapy exists, the patient must be disease-free for at least 5 years before transplantation
- If a history of renal cell carcinoma exists, patient must be disease-free for at least 2 years before transplantation
- Ability to provide informed consent. For children under the age of 7 years, only the parent can provide consent. For children aged 7–12 years, the parental or legally responsible person must provide informed consent and the minor must sign an assent. In the case of a minor between ages 13 and 18 years, the minor and parent(s) must provide informed consent
- Female candidates of child-bearing potential must have a negative serum human chorionic gonadotropin chain beta pregnancy test 14 days before transplantation. All candidates must practice barrier contraception

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*Frasetto, Stock: Nat.Rev. Nephrology 2009*
SUMMARY

- Renal transplantation is both safe and effective in patients with HIV
- Rejection rates are increased in patients with HIV
- Monitor for drug-interactions
- Co-infection with Hep C is challenging

Trullas et al, KI 2010
# Renal Transplantation between HIV-Positive Donors and Recipients

**Table 1. Clinical Characteristics of HIV-Positive Recipients of a Transplant from an HIV-Positive Donor.**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Patient 3</th>
<th>Patient 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>47</td>
<td>56</td>
<td>37</td>
<td>29</td>
</tr>
<tr>
<td>Sex</td>
<td>Male</td>
<td>Male</td>
<td>Male</td>
<td>Female</td>
</tr>
<tr>
<td><strong>Before transplantation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diagnosis on renal biopsy</td>
<td>HIV-associated nephropathy</td>
<td>HIV-associated nephropathy and hypertensive nephropathy</td>
<td>Malignant hypertension</td>
<td>HIV-associated nephropathy</td>
</tr>
<tr>
<td>Creatinine (μmol/liter)</td>
<td>678</td>
<td>582</td>
<td>1712</td>
<td>725</td>
</tr>
<tr>
<td>CD4 count (cells/mm$^3$)</td>
<td>288</td>
<td>258</td>
<td>132</td>
<td>147</td>
</tr>
<tr>
<td>HIV viral load (copies/ml)</td>
<td>&lt;50</td>
<td>&lt;50</td>
<td>&lt;50</td>
<td>&lt;50</td>
</tr>
</tbody>
</table>

| CD4 count (cells/mm$^3$)        |           |           |           |           |
| At 6 mo                         | 129       | 113       | 140       | 140       |
| At 12 mo                        | 253       | 119       | 112       | 220       |
| HIV viral load (copies/ml)      |           |           |           |           |
| At 6 mo                         | <50       | <50       | <50       | <50       |
| At 12 mo                        | <50       | <50       | <50       | <50       |
| Creatinine (μmol/liter)         |           |           |           |           |
| At 6 mo                         | 114       | 119       | 181       | 101       |
| At 12 mo                        | 87        | 104       | 85        |           |
| Diagnosis on renal biopsy       |           |           |           |           |
| At 3 mo                         | Normal kidney | Normal kidney | Acute tubular necrosis | Normal kidney |
| At 9 mo                         | Normal kidney | Calcineurin toxicity | Early collapsing glomerulonephritis | Normal kidney |
Association of Trypanolytic ApoL1 Variants with Kidney Disease in African Americans

Giulio Genovese,1,2,* David J. Friedman,1,3* Michael D. Ross,4 Laurence Lecordier,5 Pierrick Uzureau,5 Barry I. Freedman,6 Donald W. Bowden,7,8 Carl D. Langeland,6,9 Taras K. Oleksyk,10 Andrea L. Uscinski Knob,11 Andrea J. Bernhardt,1 Pamela J. Hicks,7,8 George W. Nelson,11 Benoît Vanhollebeke,5 Cheryl A. Winkler,12 Jeffrey B. Kopp,13 Etienne Pays,5† Martin R. Pollak1,13†

Science, 2010

<table>
<thead>
<tr>
<th></th>
<th>Average Lifetime Risk</th>
<th>0 Kidney Risk Variants</th>
<th>1 Kidney Risk Variant</th>
<th>2 Kidney Risk Variants</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV-CG (without antiretroviral therapy)</td>
<td>10%</td>
<td>0% (0, 6)</td>
<td>5% (3, 8) 1:20</td>
<td>20% (15, 25) 1:5</td>
</tr>
<tr>
<td>FSGS</td>
<td>0.8%</td>
<td>0.2% (0.1, 0.4) 1:500</td>
<td>0.4% (0.3, 0.5) 1:250</td>
<td>1.6% (1.4, 1.8) 1:62</td>
</tr>
<tr>
<td>Hypertension-attributed ESKD</td>
<td>2.25%</td>
<td>1.4% (1, 1.7) 1:71</td>
<td>1.9% (1.7, 2.1) 1:53</td>
<td>3.1% (2, 3.3) 01:32</td>
</tr>
</tbody>
</table>

NOTE. Lifetime risks were estimated, as described in the text, for 0, 1, and 2 copies of the MYH9 E-1 kidney risk variant. Numbers in parentheses are 95% confidence intervals.
Role of Donor Genetics and Recipient Genetics in Kidney Transplant Outcomes

This study is currently recruiting participants.
Verified December 2011 by National Institutes of Health Clinical Center (CC)

First Received on June 11, 2010. Last Updated on March 20, 2012  
History of Changes

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