HIV and AIDS
Learning Objectives

• Discuss the criteria for kidney transplant in patients with ESRD and HIV
• Describe outcomes in patients with HIV undergoing kidney transplant
• Explain potential drug interactions with ARV therapy and immunosuppression
• Describe ethical issues regarding HIV and kidney transplant
Death rates for HIV disease for all ages

NOTE: HAART is highly active antiretroviral therapy.
SOURCE: CDC/NCHS, Health, United States, 2013. Figure 24. Data from the National Vital Statistics System.
HIV: A Chronic Disease

- People living with HIV
- New HIV infections using back-calculation methodology
- New HIV infections using original incidence surveillance methodology
- New HIV infections using updated incidence surveillance methodology

Timeline (1980-2010):
- 1980: 100,000
- 1983: 300,000
- 1986: 500,000
- 1989: 700,000
- 1992: 900,000
- 1995: 1,100,000
- 1998: 1,300,000
- 2001: 1,500,000
- 2004: 1,700,000
- 2007: 1,900,000
- 2010: 2,100,000
Estimated New HIV Diagnoses in US

- Black MSM: 11,201
- White MSM: 9,008
- Hispanic/Latino MSM: 7,552
- Black Heterosexual Women: 4,654
- Black Heterosexual Men: 2,108
- Hispanic/Latina Heterosexual Women: 1,159
- White Heterosexual Women: 1,115
HIV and Kidney Disease

• Multifactorial:
  – Immune-mediated GN
  – HIVAN
    • Most common cause in untreated blacks
    • 3rd leading cause of ESRD in blacks
  – Drug induced (ART, antimicrobials)
  – Nonreversible AKI
  – TMA
  – cART associated with increase in DM and HTN
Prevalence of HIV in Dialysis Centers

<table>
<thead>
<tr>
<th>Country (reference)</th>
<th>Year</th>
<th>Total number of patients on dialysis</th>
<th>Prevalence of HIV infection (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>United States $^{10}$</td>
<td>1985</td>
<td>ND</td>
<td>0.3</td>
</tr>
<tr>
<td></td>
<td>2002</td>
<td>263,820</td>
<td>1.5</td>
</tr>
<tr>
<td>Europe $^{11,12}$</td>
<td>1984–1986</td>
<td>$&gt;4000$</td>
<td>0–5</td>
</tr>
<tr>
<td></td>
<td>1990</td>
<td>152,658</td>
<td>0.12</td>
</tr>
<tr>
<td>Italy $^{13}$</td>
<td>1990</td>
<td>21,500</td>
<td>0.11</td>
</tr>
<tr>
<td></td>
<td>1995</td>
<td>27,000</td>
<td>0.13</td>
</tr>
<tr>
<td>France $^{14,15}$</td>
<td>1997</td>
<td>22,707</td>
<td>0.36</td>
</tr>
<tr>
<td></td>
<td>2002</td>
<td>27,577</td>
<td>0.67</td>
</tr>
<tr>
<td>Spain $^{16,17}$</td>
<td>2004</td>
<td>4962</td>
<td>1.15</td>
</tr>
<tr>
<td></td>
<td>2006</td>
<td>14,876</td>
<td>0.54</td>
</tr>
<tr>
<td>Egypt $^{18}$</td>
<td>1991</td>
<td>5000</td>
<td>1.64</td>
</tr>
<tr>
<td>Japan $^{19}$</td>
<td>1986</td>
<td>1314</td>
<td>0</td>
</tr>
<tr>
<td>Brazil $^{20}$</td>
<td>1986</td>
<td>132</td>
<td>14</td>
</tr>
</tbody>
</table>

Abbreviations: HIV, human immunodeficiency virus; ND, no data available.
Survival of HIV Patients on RRT

- Increased over last 2 decades
- Mortality approaching that for ESRD in general population
- Survival rates at 1, 3, and 5 years of 95.2%, 71.7%, and 62.7%
  - Introduction of cART
  - Treatment of Ois
  - Enhanced dialysis procedures
HIV and Transplant

• HIV previously absolute contraindication
  – Post-transplant IS could accelerate HIV disease and increase risk for OIs
  – 1\textsuperscript{st} experiences in ESLD patients with HCV co-infection and cirrhosis

• KTx is a valid option in selection HIV patients with kidney disease
# of Kidney Transplants Performed

Locke et al 2015; 26: 2222-2229
Case Presentation

- 47 year old male presents for kidney transplant evaluation
- HIV diagnosed in 1989 and acquired through sexual contact
- Complications include Pneumocystis pneumonia and anal condyloma
- Maintained on Kaletra, Ziagen, Epivir, Viread
Case Presentation

• PMH
  – Hypertension x 10 years
  – ESRD on HD x 3 years
  – Hepatitis C (6 million copies in blood; biopsy with grade 2 activity, no fibrosis)
  – Seizure disorder
  – Anemia
## Case Presentation

<table>
<thead>
<tr>
<th>Date</th>
<th>CD4 count</th>
<th>HIV viral load</th>
</tr>
</thead>
<tbody>
<tr>
<td>11/2014</td>
<td>546 cell/cu_mm</td>
<td>Target not detected</td>
</tr>
<tr>
<td>08/2014</td>
<td>374 cell/cu_mm</td>
<td>Target not detected</td>
</tr>
<tr>
<td>04/2014</td>
<td>540 cell/cu_mm</td>
<td>Target not detected</td>
</tr>
<tr>
<td>12/2013</td>
<td>250 cell/cu_mm</td>
<td>Target not detected</td>
</tr>
<tr>
<td>11/2000</td>
<td>13 cell/cu_mm</td>
<td>235,604 copies/mL</td>
</tr>
</tbody>
</table>
Questions

• Is he a candidate for kidney transplantation?
• What are survival outcomes of kidney transplant recipients with HIV?
• What immunosuppression regimen should be used and will the medications interact with his ARV therapy?
• He would like to know if his partner with HIV could be considered as a potential live donor?
Criteria for Transplantation

**INCLUSION CRITERIA**
- Same standard criteria as HIV – patients
- Undetectable HIV VL for 3 months
- CD4 counts > 200 for 6 months
- Tolerating a stable ART regimen for 3 months before transplant
- Opportunistic infections including PJP, MAC, and CMV that occurred while not on ART therapy
- Hepatitis C and/or hepatitis B without significant liver fibrosis on biopsy
- Ready access to drug level monitoring

**EXCLUSION CRITERIA**
- Same standard as HIV- patients
- History of PML, cryptosporidiosis or visceral Kaposi’s sarcoma
Questions

• Is he a candidate for kidney transplantation?
• What are the survival outcomes of kidney transplant recipients with HIV?
• What immunosuppression regimen should be used and will the medications interact with his ARV therapy?
• He would like to know if his partner with HIV could be considered as a potential live donor?
HIV and Kidney Transplant Outcomes

• NIH funded, non-randomized trial conducted between Nov 2003-June 2009
• 150 HIV+ patients at 19 transplant centers
• Median follow-up was 1.7 years
• Induction allowed (32% received thymo)
• 3 drug maintenance regimen
• All received ID prophylaxis
Survival Outcomes After KTX

1-year 95%
3-year 88%

Survival Outcomes After KTX

B. Graft Survival

1-year 90%
3-year 74%

![Graph showing survival outcomes after KTX with data points and lines for different groups: SRTR (all), SRTR (≥65 yr), HIV-infected (this study).]

<table>
<thead>
<tr>
<th>No. at Risk</th>
<th>Year 1</th>
<th>Year 2</th>
<th>Year 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>SRTR (all)</td>
<td>29,064</td>
<td>16,114</td>
<td>6215</td>
</tr>
<tr>
<td>HIV-infected (this study)</td>
<td>93</td>
<td>64</td>
<td>31</td>
</tr>
<tr>
<td>SRTR (≥65 yr)</td>
<td>4,103</td>
<td>2,133</td>
<td>807</td>
</tr>
</tbody>
</table>

Acute Rejection Rates

C  Time to First Acute Allograft Rejection

1-year 31%
3-year 41%

No. at Risk
HIV-infected (this study) 63 41 19

Summary of Study Results

• No evidence of accelerated HIV disease progression or associated complications

• Higher than expected rates of rejection
  – Achieving therapeutic and nontoxic IS levels
  – Increased with CsA over FK use
  – Memory response
    • Allosensitization
    • Increased responsiveness of the T cell
    • Prior infections can lead to generation of memory alloreactive T cells
Patient Survival with KTX as Compared to Remaining on Dialysis

- 65 HIV+ patients received transplant and 67 HIV+ patients remained on wait list
  - Transplant recipients
    - 1-year 91%
    - 3-year 80%
  - Wait list patients
    - 1-year 89%
    - 3-year 26%

Kumar et al. AJT 2008; 8(suppl 2): 179
National Cohort of HIV+ Transplant Recipients

• 510 HIV+ kidney transplant recipients compared to 94,948 HIV- recipients over time period of 2002-2011

• Matched 1:10 to HIV- controls

• Median follow-up was 3.8 years

• HIV+ recipients
  – Younger, lower BMI, male, African American, co-infected with hepatitis C, receive maintenance steroids, increased rejection rates, fewer living donors

Locke et al. JASN 2015; 26: 2222-2229
National Cohort of HIV+ Transplant Recipients

Locke et al. JASN 2015; 26: 2222-2229
National Cohort of HIV+ Transplant Recipients

Locke et al. JASN 2015; 26: 2222-2229
HCV/HIV Coinfection

• HIV/HCV co-infected recipients with worse outcomes in both studies
• No adjustment for donor risk factors
• Xia et al. evaluated outcomes in paired deceased donor kidneys
  – HCV+, n=1700; HIV+, n=243
  – HCV-, n=1700; HIV-, n=243
  – Of cohort, 36 HCV+/HIV+
Effect of HCV/HIV Coinfection in KTX

Xia et al. AJT 2014; 14: 2037-2047
Effect of HCV/HIV Coinfection in KTX

Product-Limit Survival Estimates
With Number of Subjects at Risk

Survival Probability

Death-Censored Graft Survival (Months)

HIV-/HCV-
HIV+/HCV-
HIV+/HCV+

Logrank p=0.0737

Xia et al. AJT 2014; 14: 2037-2047
Effect of HCV/HIV Coinfection in KTX

• HCV is strong predictor of poorer patient and graft survival and more evident with coinfection
• May exacerbate the effect of HCV on allograft
  – Mediated by HCV PCR+ infection
  – Enhanced cellular and humoral responses
  – HCV also associated with PTDM, CVD, infection, liver related mortality
• Higher risk group due to behavioral risk factors
## Treatment for HCV in Patients Co-infected with HIV

<table>
<thead>
<tr>
<th>Response</th>
<th>Ledipasvir–Sofosbuvir for 12 Wk (N=335)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>no. (%)</td>
</tr>
<tr>
<td><strong>HCV RNA &lt;LLOQ</strong></td>
<td></td>
</tr>
<tr>
<td>During therapy period</td>
<td></td>
</tr>
<tr>
<td>At wk 2</td>
<td>272 (81)</td>
</tr>
<tr>
<td>At wk 4</td>
<td>331 (99)</td>
</tr>
<tr>
<td>After end of therapy</td>
<td></td>
</tr>
<tr>
<td>At wk 4</td>
<td>324 (97)</td>
</tr>
<tr>
<td>At wk 12</td>
<td>322 (96)</td>
</tr>
<tr>
<td>Virologic breakthrough during treatment</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Relapse in patients with HCV RNA &lt;LLOQ at end of therapy</td>
<td>10 (3)</td>
</tr>
<tr>
<td>Death</td>
<td>1 (&lt;1)</td>
</tr>
</tbody>
</table>

Naggie et al.  NEJM  2015; 373: 705-713
Hepatitis B Co-Infection

- r/o cirrhosis with liver biopsy
- Should be treated with NAs before transplant with negative HBV DNA
- Optimal timing for treatment initiation should be individualized

* Newer NA is entecavir, tenofovir, and telbivudine.*

Pipili et al. KI 2013; 84: 880-885
Questions

• Is he a candidate for kidney transplantation?
• What are the survival outcomes of kidney transplant recipients with HIV?
• What immunosuppression regimen should be used and will the medications interact with his ARV therapy?
• He would like to know if his partner with HIV could be considered as a potential live donor?
Acute Rejection Rates

- Cumulative AR rates
  - 1-year 52%
  - 2-year 64%
  - 3-year 73%
- Most were cellular
- Age and PRA at transplant associated with 1st rejection episode
- 39% induction therapy

Roland et al. AJT 2008; 8: 355-365
Induction Therapy with Thymoglobulin

CD4 Counts in HIV-infected Kidney Recipients

- Individual recipients
- Mean, after Thymo (n=11)
- Mean, no Thymo (n=9)

Carter et al. AJT 2006; 6: 753-760
Maintenance Immunosuppression

- CNI inhibitor, MMF and steroids
  - CsA and MMF have antiretroviral qualities
- mTOR inhibitors
  - Effective against Kaposi’s sarcoma
Figure 1. The effects of HAART and immunosuppressive medications on HIV activation and replication. CYA, cyclosporine.
Recommendations for ART in HIV+ SOT

1. HAART should be designed on an individual basis, taking into account factors such as grade of end-stage organ disease, drug interactions and, when possible, antiretroviral sensitivity testing.
2. The optimal HAART regimen in the post-transplant period is unknown.
3. Pharmacokinetic interactions between antiretrovirals, immunosuppressive agents and other drugs used during the post-transplant period play a major role in this complex clinical scenario (BII).
4. PIs and cobicistat act as CYP3A4 inhibitors and require rapid and considerable dose adjustment of immunosuppressive agents (BII).
5. NNRTIs (mainly efavirenz and nevirapine) are inducers of CYP3A4 and lead to more rapid elimination of calcineurin inhibitors, thus necessitating higher doses of these drugs (BII).
6. The integrase inhibitor raltegravir is not a substrate of cytochrome P450, thus making it safe and effective in this setting (BII). The second-generation integrase inhibitor dolutegravir could prove to be a useful therapeutic option, although data are lacking.
7. The combination of two nucleos(t)ide reverse transcriptase inhibitors (tenofovir/emtricitabine or abacavir/lamivudine) with a non-boosted integrase inhibitor (raltegravir and, probably, dolutegravir) is the antiretroviral regimen of choice in HIV-infected liver recipients (BII).

***Unique challenge in the post-transplant HIV patient is the management of drug-drug interactions***
## Antiretroviral and IS Drug Interactions

<table>
<thead>
<tr>
<th></th>
<th>Immunosuppressive drugs</th>
<th>GCs</th>
<th>AZA</th>
<th>CsA</th>
<th>FK</th>
<th>MMF</th>
<th>Siro</th>
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<td><strong>NRTI</strong>s</td>
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<tr>
<td>3TC</td>
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<td>0</td>
<td>+</td>
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<tr>
<td>D4T</td>
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<td>NA</td>
<td>NA</td>
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<tr>
<td>ddC</td>
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<tr>
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<td>ZDV</td>
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<td>NA</td>
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<tr>
<td><strong>NNRTI</strong>s</td>
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<td>DLV</td>
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<td>EFV</td>
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<tr>
<td>NVP</td>
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<tr>
<td><strong>Protease inhibitors</strong></td>
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</tr>
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<td>APV</td>
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<td>IDV</td>
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<td>LPV</td>
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<td>±</td>
<td>±</td>
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<td>NA</td>
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<td>+</td>
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</table>

Izzedine et al. KI 2004; 66: 532-541
# Antiretroviral and IS Drug Interactions

<table>
<thead>
<tr>
<th>Protease inhibitors</th>
<th>Integrase inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Strong inhibitors of CYP3A enzymes and P-gp</td>
<td>• Low risk for interactions with immunosuppressants</td>
</tr>
<tr>
<td>• Requires lower daily doses and prolonged dosing intervals for CNIs</td>
<td>• Metabolized via UGT-mediated glucuronidation</td>
</tr>
<tr>
<td>• Prolong CNI half-life by 5 – 20 fold.</td>
<td>• Beneficial effects on renal function</td>
</tr>
<tr>
<td>• PK flat line from normal peak/trough</td>
<td>• Low genetic barrier to resistance (Raltegravir).</td>
</tr>
<tr>
<td></td>
<td>• Elvitegravir: high barrier to resistance</td>
</tr>
</tbody>
</table>
# VUMC HIV+ Algorithms

## Induction Therapy

<table>
<thead>
<tr>
<th>Maintenance Immunosuppression</th>
<th>Simulect and Solumedrol</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>- Calcineurin inhibitor</td>
</tr>
<tr>
<td></td>
<td>- Non-PI based ART regimen: standard tacrolimus dosing</td>
</tr>
<tr>
<td></td>
<td>- PI based ART regimen: 0.5 mg tacrolimus X 1 dose inpatient</td>
</tr>
<tr>
<td></td>
<td>- Dose will be adjusted by transplant nephrologist in follow up clinic visits</td>
</tr>
<tr>
<td></td>
<td>- Mycophenolate mofetil (MMF) 1000 mg BID</td>
</tr>
<tr>
<td></td>
<td>- Prednisone 20mg daily tapered to 5mg daily</td>
</tr>
</tbody>
</table>

## Prophylaxis

<table>
<thead>
<tr>
<th>Prophylaxis</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>PJP prophylaxis with TMP-SMX lifelong (dapsone if sulfa allergy)</td>
<td></td>
</tr>
<tr>
<td>CMV prophylaxis with Valganciclovir 450 mg daily for 4 months if CMV D+/R+ and 6 months if CMV D+/R-</td>
<td></td>
</tr>
<tr>
<td>Toxoplasma prophylaxis with TMP-SMX if CD4 &lt;100 (dapsone if sulfa allergy)</td>
<td></td>
</tr>
<tr>
<td>MAC prophylaxis with azithromycin if CD4 &lt;75</td>
<td></td>
</tr>
</tbody>
</table>
VUMC HIV+ Transplant Outcomes

• 24 patients since 2009
  – 5 hepatitis B positive; 2 hepatitis C positive
  – 3 acute rejections
  – 1 failed graft due to BK virus
  – No deaths
  – HIV remains undetectable in all
  – No significant infections
  – Average creatinine 1.39 mg/dl
Questions

• Is he a candidate for kidney transplantation?
• What are the survival outcomes of kidney transplant recipients with HIV?
• What immunosuppression regimen should be used and will the medications interact with his ARV therapy?
• He would like to know if his partner with HIV could be considered as a potential live donor?
The Challenge in South Africa

Current dialysis population = 4,500

All HIV-infected donor organs discarded

10% of 5.5 million HIV patients = 550,000 will develop ESRD
HIV+ to HIV+ Kidney Transplant

- 27 HIV+ recipients of kidneys from HIV+ donors
  - 84% patient survival at 1 and 3 years; 74% at 5 years
  - Graft survival 93%, 84% and 84%
  - Low rates of rejection
  - HIV remain suppressed
  - 3 patients developed HIVAN

Muller et al. NEJM 2015; 372: 613-620

Elmi Mueller, Groote Schurr Hospital
# Ethical Considerations

<table>
<thead>
<tr>
<th>Access</th>
<th>Risks</th>
<th>Consent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demand for transplant coupled with lack of organs requires ways to expand access to transplant</td>
<td>Infecting an HIV+ recipient with new viral strain may lead to increased complications</td>
<td>Need to ensure patient’s decisions are informed and voluntary</td>
</tr>
<tr>
<td>Estimates suggest we may be able to increase donor pool by 500 donors per year</td>
<td>Should HIV+ organs into HIV- recipients be considered under any circumstance</td>
<td>Investigators and transplant teams may have conflicts of interest in having the patient enroll in research study</td>
</tr>
<tr>
<td>May benefit African Americans who are disproportionately impacted by HIV/HIVAN</td>
<td>May put intimate partners at risk</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Significant efforts required to prevent accidental transmission</td>
<td></td>
</tr>
<tr>
<td></td>
<td>No experience with HIV+ living donors</td>
<td></td>
</tr>
</tbody>
</table>
HIV Organ Policy Equity (HOPE) Act

Signed into law on November 21, 2013 and overturned 1988 ban on use of organs from HIV+ donors
HIV Organ Policy Equity (HOPE) Act

- DHHS was required to revise federal ban on HIV+ organ donors
- OPTN was required to revise standards of quality to include policies for donated HIV+ organs ("open variance")
  - Transplant centers who want to participate must apply to join variance, supply IRB approval and submit regular data monitoring safety reports
- DHHS charged with developing guidelines for clinical research
NCT02602262

- Evaluate safety of HIV+/HIV+ kidney and liver transplantation
- Assess survival benefit of accepting an HIV+ organ compared with waiting for an HIV- donor
- Hopkins has performed first HIV+/HIV+ kidney transplant in the U.S. and the first HIV+/HIV+ liver transplant in the world
Summary

Kidney transplantation in patients with HIV infection is a viable therapeutic option
Ideal immunosuppressive regimen remains uncertain
Higher rates of rejection are reported in clinical trials
Immunosuppressive therapy does not seem to negatively impact the course of HIV infection
Some immunosuppressive drugs may exert antiretroviral actions
Special attention should be paid to the potential interaction between ART and immunosuppressive drugs
A close collaboration between infectious disease specialists and transplant professionals is mandatory in order to optimize transplantation outcomes in these patients
Transplantation from HIV+ donors to HIV+ is currently being researched