New hope for patients with HIV: Solid organ transplant from HIV-positive donors

Pharmacy Grand Rounds - February 21, 2017
Melissa Laub, PharmD
PGY1 Pharmacy Resident
Mayo Clinic Hospital – Rochester, MN
Objectives

1. Discuss the policy changes regarding solid organ transplantation in HIV-positive patients

2. Review the literature evaluating induction and maintenance immunosuppression options for HIV-positive organ recipients

3. Describe the long term pharmacotherapy management of HIV-positive organ recipients
History of HIV and transplant

1988 • NOTA amendment banned HIV-positive donors

1996 • Combination ART became available

2013 • HOPE Act passed in the U.S.

2015 • OPTN policy and system changes to implement HOPE Act

2016 • First HIV-positive liver and kidney donor in U.S

NOTA: National Organ Transplant Act
ART: Antiretroviral therapy
HOPE: HIV Organ Policy Equity
OPTN: Organ Procurement and Transplantation Network

HOPE Act Safeguards and Research Criteria. 2015. DHHS/NIH.
In a first, HIV-positive donor's kidney, liver given to HIV-positive patients

First Transplant from HIV-Positive Donor Performed in U.S.

Johns Hopkins to Perform First H.I.V.-Positive Organ Transplants in U.S.
Balancing act

- Drug-drug interactions
- Superinfection
- Rejection
- CD4+ T-Cell Count
- Immunosuppression
- HIV viral replication
- Opportunistic infections
HOPE Act: Policy implementation

- Permits organ donation from HIV-positive donors to HIV-positive recipients
  - Under approved NIH research protocols only
  - 14 U.S. hospitals enrolled

- Outlines requirements in 6 categories:
  1. Donor eligibility
  2. Recipient eligibility
  3. Transplant hospital criteria
  4. OPO responsibilities
  5. HIV transmission prevention
  6. Outcome measures
HIV-positive donor eligibility

Living Donor

- HIV-1 RNA <50 copies/mL
- CD4+ T-cell count ≥500/mL for the previous 6-months

Deceased Donor

- No evidence of invasive opportunistic complications
- Pre-implant donor organ biopsy
- No viral load or CD4+ T-cell requirements

HOPE Act Safeguards and Research Criteria. 2015. DHHS/NIH.
Concerns: HIV-positive donors

**Viral Transmission**
- Transmission of resistant strain
- Team must describe anticipated post-transplant ART regimen
- Transplant must not be performed if doubts exist regarding ability to suppress viral replication

**Risks to Living Donors**
- Long-term risk of organ disease
  - Apolipoprotein 1 coding variants → higher risk of HIV associated nephropathy
  - Prevalence of co-infection
  - Could limit ART choices

ART: Antiretroviral therapy

HOPE Act Safeguards and Research Criteria. 2015. DHHS/NIH.
Recipient eligibility

- CD4+ T-cell counts
  - Kidney: ≥200/mL
  - Liver: ≥100/mL and no history of OI (≥200/mL if history of OI)

- HIV-1 RNA <50 copies/mL, on stable antiretroviral regimen

- No evidence of active opportunistic complications

- No history of primary CNS lymphoma or PML

OI: Opportunistic Infection
PML: progressive multifocal leukoencephalopathy

HOPE Act Safeguards and Research Criteria. 2015. DHHS/NIH.
Question

• True or false?
  Any hospital that performs organ transplant may now perform HIV-positive to HIV-positive organ transplant.

A. True
B. False
Question

• Which of the following HIV-positive recipients would be eligible for a kidney transplant based on their CD4+ T-cell (cells/mL) and HIV RNA (copies/mL), assuming they have been on a stable ART regimen and have no opportunistic infection history?

A. CD4+ 125, HIV RNA <50
B. CD4+ 270, HIV RNA <50
C. CD4+ 300, HIV RNA 500
D. CD4+ 200, HIV RNA 600
Not outlined in the HOPE Act

ART: Antiretroviral therapy
Induction overview

Signal 1: Antigen triggers T-cell receptor

Signal 2: Costimulation

Signal 3: Cytokines trigger receptors

T Cell

Calcineurin → NFAT → Cytokine induction (e.g., IL-2)

Cell Cycle

mTOR

IL-2 Receptor

CD25

ATG

Non-Depleting

Basiliximab

Depleting

APC: Antigen presenting cell
MHC: Major histocompatibility complex
Ag: Antigen
TCR: T-Cell receptor
NFAT: Nuclear factor of activated T-Cells
IL-2: Interleukin 2
mTOR: Mammalian target of rapamycin
ATG: Antithymocyte globulin

Image adapted from:
Maintenance immunosuppression overview

**Signal 1:** Antigen triggers T-cell receptor

**Signal 2:** Costimulation

**Signal 3:** Cytokines trigger receptors

- **APC:** Antigen presenting cell
- **MHC:** Major histocompatibility complex
- **Ag:** Antigen
- **TCR:** T-Cell receptor
- **NFAT:** Nuclear factor of activated T-Cells
- **IL-2:** Interleukin 2
- **mTOR:** Mammalian target of rapamycin
- **ATG:** Antithymocyte globulin
- **CD52:** Receptor
- **CD25:** Receptor
- **mTOR inhibitors**
- **Calcineurin inhibitors**
- **Corticosteroids**
- **Cytokine induction (e.g., IL-2)**
- **Costimulation blocker**
- **Antiproliferatives**
- **Basiliximab**

Image adapted from:
Antiretroviral therapy overview

- At least 3 agents from 2 distinct classes
  - Most common is 2 NRTIs + 1 PI or 1 Integrase inhibitor

NNRTI: Non-nucleoside reverse transcriptase inhibitor
NRTI: Nucleoside reverse transcriptase inhibitors
PI: protease inhibitor

### HIV-negative to HIV-positive kidney transplants

<table>
<thead>
<tr>
<th>Design</th>
<th>• Prospective, non-randomized</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population</td>
<td>• Recipients (n=150): HIV-positive kidney</td>
</tr>
<tr>
<td>Comparator</td>
<td>• SRTR overall and ≥ 65 years old</td>
</tr>
<tr>
<td>Primary outcomes</td>
<td>• Patient survival and graft survival</td>
</tr>
</tbody>
</table>

#### Immunosuppression at 1 week

<table>
<thead>
<tr>
<th>Medication</th>
<th>Value no. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tacrolimus</td>
<td>99 (66)</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>33 (22)</td>
</tr>
<tr>
<td>Mycophenolate mofetil</td>
<td>131 (87)</td>
</tr>
<tr>
<td>Basiliximab or daclizumab</td>
<td>76 (51)</td>
</tr>
<tr>
<td>Antithymocyte globulin</td>
<td>48 (32)</td>
</tr>
</tbody>
</table>

#### ART Regimen

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Value no. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PI-based</td>
<td>63 (42)</td>
</tr>
<tr>
<td>NNRTI-based</td>
<td>59 (39)</td>
</tr>
<tr>
<td>CD4+ T-cells/mL</td>
<td>524 (IQR 385-672)</td>
</tr>
</tbody>
</table>

**ART:** Antiretroviral therapy; **PI:** Protease inhibitor; **NNRTI:** Non-nucleoside reverse transcriptase inhibitor; **SRTR:** Scientific Registry of Transplant Recipients

HIV-negative to HIV-positive kidney transplants

**Patient Survival**

<table>
<thead>
<tr>
<th>Timeframe</th>
<th>Rejection Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Study Patients</td>
</tr>
<tr>
<td>1 year</td>
<td>31%</td>
</tr>
<tr>
<td>3 years</td>
<td>41%</td>
</tr>
</tbody>
</table>

**Graft Survival**

SRTR: Scientific Registry of Transplant Recipients
ATG: Antithymocyte globulin

Acute rejection in HIV-positive transplant

- Immune dysregulation in HIV
- HLA captured by HIV cells
- Drug-drug interactions
- Induction regimens
### Induction: HIV-positive recipients

<table>
<thead>
<tr>
<th>Design</th>
<th>Retrospective</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population</td>
<td>HIV-positive kidney recipients (n=830) in SRTR</td>
</tr>
<tr>
<td>Comparator</td>
<td>Matched cohort of HIV-negative kidney recipients</td>
</tr>
<tr>
<td>Primary outcomes</td>
<td>Time to first infection, categorized based on type of induction</td>
</tr>
</tbody>
</table>

#### Graph

**Percent Received**

<table>
<thead>
<tr>
<th>Induction category</th>
<th>HIV+ KT</th>
<th>HIV- KT</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Induction</td>
<td>30.4</td>
<td>20.8</td>
</tr>
<tr>
<td>Anti-IL2R only</td>
<td>32.3</td>
<td>17.2</td>
</tr>
<tr>
<td>ATG only</td>
<td>22.8</td>
<td>4.9</td>
</tr>
<tr>
<td>Anti-IL2R + ATG</td>
<td>9.6</td>
<td>4.2</td>
</tr>
<tr>
<td>Other</td>
<td>42.1</td>
<td>15.7</td>
</tr>
</tbody>
</table>

**Note:**
- **SRTR:** Scientific Registry of Transplant Recipients
- **ATG:** Antithymocyte globulin
- **KT:** Kidney transplant
- **IL-2 R:** Interleukin 2 receptor

## Induction: HIV-positive recipients

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Induction (Compared to no induction)</th>
<th>HR or RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infection</td>
<td></td>
<td>0.80 (0.55-1.18)</td>
</tr>
<tr>
<td>Graft loss</td>
<td></td>
<td>0.47 (0.24-0.89)</td>
</tr>
<tr>
<td>DGF</td>
<td></td>
<td>0.66 (0.51-0.84)</td>
</tr>
<tr>
<td>Hospital LOS during first year</td>
<td></td>
<td>0.70 (0.52-0.95)</td>
</tr>
<tr>
<td>Mortality</td>
<td></td>
<td>0.60 (0.24-1.28)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Outcome</th>
<th>ATG (Compared to no induction)</th>
<th>HR or RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infection</td>
<td></td>
<td>0.87 (0.54-1.39)</td>
</tr>
<tr>
<td>Acute Rejection</td>
<td></td>
<td>0.59 (0.35-0.99)</td>
</tr>
</tbody>
</table>

**KT**: Kidney transplant  
**ATG**: Antithymocyte globulin  
**LOS**: Length of stay  
**DGF**: Delayed graft function  
**HR**: Hazard ratio  
**RR**: Relative risk  
**CI**: Confidence interval  

Other studies

• Viral suppression of > 2 years may decrease chance of acute rejection

• Recipient CD4+ T-cell count of > 350 cell/mL may decrease risk of infection

**HIV-positive to HIV-positive kidney transplants**

<table>
<thead>
<tr>
<th>Design</th>
<th>• Prospective, non-randomized</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Population</strong></td>
<td><strong>Recipients (n=27):</strong></td>
</tr>
<tr>
<td>Recipients</td>
<td>• HIV-positive kidney</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Comparator</strong></td>
<td>• HIV-negative recipients in same unit</td>
</tr>
<tr>
<td><strong>Immunosuppression</strong></td>
<td>• Antithymocyte globulin induction</td>
</tr>
<tr>
<td>Regimen</td>
<td>• Maintenance starting day 0</td>
</tr>
<tr>
<td></td>
<td>• Antithymocyte globulin induction</td>
</tr>
<tr>
<td></td>
<td>• Maintenance starting day 0</td>
</tr>
<tr>
<td>ART Regimen</td>
<td>Initial</td>
</tr>
<tr>
<td></td>
<td>• NNRTI-based first-line → boosted PI-based regimen</td>
</tr>
<tr>
<td></td>
<td>Concerns regarding calcineurin-inhibitor toxicity</td>
</tr>
<tr>
<td></td>
<td>• Continue pretransplantation regimen</td>
</tr>
<tr>
<td><strong>Primary outcomes</strong></td>
<td>• Patient survival</td>
</tr>
<tr>
<td></td>
<td>• Graft survival</td>
</tr>
</tbody>
</table>

NNRTI: Non-nucleoside reverse transcriptase inhibitor  
PI: protease inhibitor  

### HIV-positive to HIV-positive kidney transplants

<table>
<thead>
<tr>
<th>Demographic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recipients (n=27)</td>
<td></td>
</tr>
<tr>
<td>Age – yr</td>
<td>41 (IQR 39-43)</td>
</tr>
<tr>
<td>Male</td>
<td>15 (56%)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>26 (96%)</td>
</tr>
<tr>
<td>ART Regimen</td>
<td></td>
</tr>
<tr>
<td>PI-based</td>
<td>11 (41%)</td>
</tr>
<tr>
<td>NNRTI-based</td>
<td>16 (59%)</td>
</tr>
<tr>
<td>CD4+ T-cells/mL</td>
<td>288 (IQR 236-511)</td>
</tr>
</tbody>
</table>

NNRTI: Non-nucleoside reverse transcriptase inhibitor  
PI: Protease inhibitor  
IQR: Interquartile range  

HIV-positive to HIV-positive kidney transplant

Patient Survival  Graft Survival

<table>
<thead>
<tr>
<th>Timeframe</th>
<th>Median CD4+ T-Cell</th>
<th>Rejection Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 year</td>
<td>179/mL (IQR 141-310)</td>
<td>8%</td>
</tr>
<tr>
<td>3 years</td>
<td>386/mL (IQR 307-484)</td>
<td>22%</td>
</tr>
</tbody>
</table>

Limitations

- Small sample size
- Population health
- Different practice standards
- Immunosuppressant levels not reported
- Only deceased donors
<table>
<thead>
<tr>
<th>Transplant year</th>
<th>U.S.</th>
<th>Switzerland</th>
<th>U.K.</th>
</tr>
</thead>
<tbody>
<tr>
<td>2016</td>
<td>2016</td>
<td>2015</td>
<td>2011</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Publication year</th>
<th>-</th>
<th>2016</th>
<th>2016</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Publication</th>
<th>News articles</th>
<th>AJT: Case report</th>
<th>NEJM: Letter to editor</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Immuno-suppression</th>
<th>-</th>
<th>Basiliximab Tacrolimus + MMF</th>
<th>Tacrolimus + MMF</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>ART regimen</th>
<th>-</th>
<th>NNRTI-based, added integrase inhibitor and temporarily entry inhibitor</th>
<th>No change, NNRTI-based</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>-</th>
<th>Continued HIV viral suppression No rejection reported</th>
<th>Transient HIV viral increase No rejection reported</th>
</tr>
</thead>
</table>
Question

• Which of the following is true regarding HIV+ to HIV+ solid organ transplant?

A. Outcomes are comparable to HIV- to HIV+ transplant and other high risk HIV- populations

B. Induction should never be used

C. Acute rejection rates are lower than HIV-recipients

D. Outcomes are worse than HIV- to HIV+ transplant
Conclusions from the literature

• Carefully select recipients and donors
• Kidney transplantation from HIV-positive donors is comparable to HIV-negative donors
• Acute rejection risk may be higher in HIV-positive recipients
  • Exact reason unclear
  • Induction should be considered
  • Be cautious with drug-drug interactions
Drug-drug interactions with ART

<table>
<thead>
<tr>
<th>Antiretroviral Therapies</th>
<th>CYP3A4 Inhibition</th>
<th>CYP3A4 Induction</th>
</tr>
</thead>
<tbody>
<tr>
<td>PIs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Boosters</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ritonavir (added to PIs)</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Cobicistat (added to elvitegravir)</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>NNRTIs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Efavirenz</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Etravirine</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Nevirapine</td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Immunosuppressant</th>
<th>CYP3A4 Substrate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcineurin Inhibitors</td>
<td></td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>X</td>
</tr>
<tr>
<td>Tacrolimus</td>
<td>X</td>
</tr>
<tr>
<td>MTOR Inhibitors</td>
<td></td>
</tr>
<tr>
<td>Sirolimus</td>
<td>X</td>
</tr>
<tr>
<td>Everolimus</td>
<td>X</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>X</td>
</tr>
</tbody>
</table>

Average tacrolimus dose + ritonavir:
0.5 mg every 7 – 10 days

Average tacrolimus dose + NNRTI:
8.5 mg BID

NNRTI: Non-nucleoside reverse transcriptase inhibitor
PI: protease inhibitor

ART with low interaction potential

<table>
<thead>
<tr>
<th>Antiretroviral Therapies</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>NRTIs</td>
<td>No CYP3A4 interaction expected</td>
</tr>
<tr>
<td>Entry Inhibitors</td>
<td>Maraviroc – PgP and CYP3A4 substrate</td>
</tr>
<tr>
<td>Enfuvirtide</td>
<td>Maraviroc – PgP and CYP3A4 substrate</td>
</tr>
<tr>
<td>Enfuvirtide</td>
<td>Maraviroc – PgP and CYP3A4 substrate</td>
</tr>
<tr>
<td>Maraviroc</td>
<td>Maraviroc – PgP and CYP3A4 substrate</td>
</tr>
<tr>
<td>Integrase Inhibitors</td>
<td>No CYP3A4 interaction expected (*Except cobicistat added to elvitegravir)</td>
</tr>
<tr>
<td>Raltegravir</td>
<td>Raltegravir</td>
</tr>
<tr>
<td>Dolutegravir</td>
<td>Raltegravir</td>
</tr>
<tr>
<td>Elvitegravir</td>
<td>Raltegravir</td>
</tr>
</tbody>
</table>

NRTI: Nucleoside reverse transcriptase inhibitor
PI: protease inhibitor

Question

• Which of the following should be avoided with calcineurin inhibitors (if possible)

A. Protease inhibitors (PIs)
B. Nucleoside reverse transcriptase inhibitors (NRTIs)
C. Ritonavir
D. A and C
E. A, B, and C
Infectious disease prophylaxis: Transplant

• Specific protocols based on center, organ, patient risk
• General prophylaxis considerations
  • Bacterial
    • Surgical site
    • Donor-derived infections
  • Viral
    • Cytomegalovirus
    • Herpes simplex virus
  • Fungal
    • *Pneumocystis jirovci* pneumonia (PCP/PJP)
    • *Candida*
    • *Aspergillus*

Infectious disease prophylaxis: HIV

CD4 <200 cells/mL
Or CD4 <14%
  - *Pneumocystis* pneumonia
    - >200 for 3 months

CD4 <100 cells/mL
  - Toxoplasmosis
    - >200 for 3 months

CD4 <50 cells/mL
  - MAC
    - >100 for 3 months

Protocol-specific organ transplant prophylaxis

MAC: *Mycobacterium avium* complex

Future research

• Other organs as experience increases
• Optimal induction, maintenance, and antiretroviral regimens
• Longer-term data in recipients and living donors
• Transmission risk of resistant HIV viral strains
• Potential for HIV-positive to HIV-negative transplant
Summary

Induction
- Benefit of induction may outweigh risk
- ATG induction may be more effective

Immunosuppression
- CNI + MMF + Steroid = Most studied regimen
- Be vigilant about CNI interactions

Antiretroviral Therapy
- PI, ritonavir, cobicistat = CYP3A4 inhibition
- NNRTI = CYP3A4 induction
- Integrase inhibitor regimen might be most ideal

Infection Prophylaxis
- Transplant protocols still followed
- Also consider CD4+ T-cell count recommendations

ATG: Antithymocyte globulin
CNI: Calcineurin inhibitor
MMF: Mycophenolate mofetil
NNRTI: Non-nucleoside reverse transcriptase inhibitor
PI: protease inhibitor
Resources

- ART interactions
  - www.HIV-druginteractions.org
  - DHHS guidelines (Tables 17-20)

- Mayo transplant resources
  - http://intranet.mayo.edu/charlie/transplant-center-rst/three-site-protocols/
  - Transplant specialists

- Mayo HIV resources
  - HIV clinic specialists
Questions

“Now, I have an opportunity to share with others living with HIV that there is hope. There is a chance. And to stay positive. I also have a chance to tell others who are living with HIV that they have an amazing opportunity. They have the power to save a life by registering to be an organ donor. Someone saved mine, and it is an incredible blessing.”

- HIV-positive to HIV-positive organ recipient at University of Alabama