New Frontiers in Solid Organ Transplantation and HIV Infection

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Learning Objectives

After attending this presentation, learners will be able to:

▪ Recognize which HIV+ patients are appropriate candidates for referral for transplant
▪ Modify antiretroviral therapy in order to minimize interactions with transplant immunosuppression
▪ Discuss the pros and cons of treating hepatitis C infection in transplant candidates

Outline

▪ Growing need for transplant
▪ Outcomes: kidney and liver transplant
▪ Management challenges: HCV, rejection, drug interactions, transplant infections
▪ HIV to HIV transplantation: HOPE in Action
Kidney disease in HIV infection

- 10-30% prevalence of chronic kidney disease
- HIV-associated nephropathy, hepatitis B/C associated nephropathy
- Antiretroviral toxicity
- Hypertension, diabetes, cardiovascular
- About 1.5% of individuals on dialysis
- More than 10,000 HIV+ individuals on dialysis

Liver disease in HIV infection

- Hepatitis B, C
- Alcoholic and non-alcoholic fatty liver disease
- 13% of all deaths due to liver disease

High mortality for those with HIV and ESRD

US 1999-2012
N = 10,526
10 year survival
HIV+ vs HIV-
63% vs. 23%
HIV+ dx of HIV-associated nephropathy

Lucas G/Kalayjian R. CID 2014; SRTR data
Smith/Lundgren. DAD study group. Lancet 2014.
High mortality for those with HIV and ESLD

Mortality on liver wait-list
At one yr HIV+ 36% vs HIV-15%
Ragni M/Fung J. Liver Transplantation. 2005

• Less access to transplant
At one yr HIV+ 36% transplanted vs HIV-47%

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NIH TR Study: HIV+ kidney transplant

N = 150
CD4 > 200, VL < 50
Median age: 46
Black: 70%
Male: 80%
HIV-AN: 25%
Hypertension: 25%
Diabetes: 9%

Patient survival
1 yr: 95%
3 yr: 91%
4 yr: 89%

Graft survival
1 yr: 90%
3 yr: 77%
4 yr: 70%

NIH TR Study: HIV+ kidney transplant

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Graft survival
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SRTR: HIV+ kidney transplant, long term outcomes

Kidney
N = 514
Matched HIV- 1:10
Race, age, sex, BMI, PRA, induction, steroids, donor age, cold ischemia time
Patient and graft survival through 10 years

Locke JI, Segov DL. JASN, 2015.
SRTR: HIV+ kidney transplant, long term outcomes

Kidney
N = 514
Matched HIV-
Patient survival
HIV+ HIV-
5 yr: 89% 89%
10 yr: 64% 78%
p=.10

NIH: HIV+/HCV+ liver transplant

HIV/HCV HCV
N = 89 N = 325
CD4 > 100
VL – any allowed*


NIH: HIV+/HCV+ liver transplant

HIV/HCV HCV
N = 89 N = 325
CD4 > 100
VL – any allowed*
Median age: 49
White: 65%
Male: 75%
Liver cancer: 35%
 Decompensated liver disease: 65%

NIH: HIV+/HCV+ liver transplant

<table>
<thead>
<tr>
<th>HIV/HCV</th>
<th>HCV</th>
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<tbody>
<tr>
<td>N = 89</td>
<td>N = 235</td>
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**Patient survival**
- 1 yr: 76% 92%
- 3 yr: 60% 79%

**Graft survival**
- 1 yr: 72% 88%
- 3 yr: 53% 74%


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HCV Treatment in Transplant

DAAs are effective, well-tolerated with minimal drug interactions
- Patients on dialysis: cure rates 95-100%
- Transplant recipients: cure rates 95-100%
- Treatment experienced, cirrhotic patients: lower
Benefits

• Prevent progression of liver disease
• Prevent HCV complications e.g. fibrosing cholestatic hepatitis or immune complex glomerulonephritis

Risks

• Exclude HCV+ donors: impact on wait time
• Harder to cure in patients with cirrhosis
• If relapse, risk of RAS HCV variants

HCV Treatment in Transplant – Pre or Post?

Benefits

• Prevent progression of liver disease
• Prevent HCV complications e.g. fibrosing cholestatic hepatitis or immune complex glomerulonephritis

Risks

• Exclude HCV+ donors: impact on wait time
• Harder to cure in patients with cirrhosis
• If relapse, risk of RAS HCV variants

What’s the answer in practice?

• No guidelines
• Strongly consider waiting for kidney transplant candidates
• For low MELD liver candidates, consider treating
• For high MELD liver candidates, consider waiting
INDUCTION

**Anti-thymocyte globulin**

**IL2 receptor blocker:**
- Basiliximab
- Daclizumab

**OR**

**Immunosuppression after transplant**

**Steroids**

**Liver**

**Calcineurin inhibitors:**
- Cyclosporine, tacrolimus

**MAINTENANCE**

**Mycophenolate mofetil**

**OR**

**mTor inhibitors:**
- Sirolimus, everolimus

**Steroids**

**NIH: Rejection in HIV+ kidney transplant**

N = 150 HIV+ KT

1 yr: 31%
3 yr: 38%
3-4 fold higher risk

NIH and SRTR: rejection in HIV+ liver transplant

NIH study:
• 39% at 3 yrs (> 50% acute cases in first few weeks)

SRTR data:
• 18% at 1 yr

Locke JE/Segev DL. Transplantation, 2016.

ART and immunosuppression interactions

MAINTENANCE
Calcineurin inhibitors: cyclosporine, tacrolimus

Drug interactions?
• Pharmacoenhancers (ritonavir, cobicistat)
  • To maintain safe troughs, very low and infrequent dosing (e.g. 0.5 mg tacrolimus/week), underexposure?

AVOID CYP3A4 INHIBITORS

SRTR: Rejection in HIV+ kidney transplant

N = 516 HIV+ KT

Rejection 1 yr:
15% HIV+ vs 8% HIV-
2 fold higher risk of rejection

Lower in those who received ATG

Post-transplant infections: NIH TR kidney transplant

Pre-transplant  | Post-transplant
---|---
Prior history of an OI  | N = 13
N = 52  |  4 Kaposi sarcoma
  • 30 PCP  |  3 PCP
  • 8 CMV  |  1 cryptosporidiosis
  • 7 MAC  |  6 candida (esophagitis 5,
  • 3 KS  |  No recurrences in patients with OI history

No survival difference with OI history

Post-transplant infections: impact of induction therapy

Infections common
  • > 50% in first year
  • Mostly UTI
  • AIDS defining ≈10%
  • Mostly CMV

No difference by induction

Trend towards fewer infections with ATG

Opportunistic infection prophylaxis – HIV TR

• PCP prophylaxis – Bactrim – indefinite
• CMV prophylaxis – valganciclovir – duration depends on donor/recipient CMV status
• MAC, histoplasmosis etc – depends on history, CD4
• Transplant ID consultation pre-transplant
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United States: HIV+ transplant over time

HIV+ Kidney Transplant

HIV+ Liver Transplant

United States: organ shortage crisis

• 116,622 individuals on the waitlist

In 2016:
• 9,975 deceased donors
• Novel donor sources are needed
• Decrease wait times for HIV+ and HIV-
South Africa: HIV D+/R+ kidney transplant

Muller et al, NEJM 2010: 362: 2336-7

HIV Organ Policy Equity Act: 2013 signed into law

• Directs the Secretary to revise current regulations (specifically, 42 CFR 121.6)
• June 2015
• Directs Secretary to publish research criteria relating to HIV+ to HIV+ transplant
• November 2015
• Requires the OPTN to revise standards for the acquisition and transportation of donated HIV+ organs
• November 2015

Implementation of the HOPE Act: late 2015
Overarching goal of HOPE in Action Studies

Learn if the use of HIV+ deceased donors in the is safe and effective

Risks of HIV D+/R+ Transplant

Challenges and Clinical Decision-Making in HIV-to-HIV Transplantation: Insights From the HIV Literature

- HIV superinfection
- HIV nephropathy
- Donor derived infections
- Rejection

Jan 2016: JHU pilot protocol (NCT02602262)
March 2016: first HOPE donor
First in US HIV D+/R+ kidney and liver transplants
20 transplant centers with active HOPE studies

NIH U01 Study: HIV+ deceased donor kidney transplant

19 US Transplant Centers
Safety and efficacy

Non-inferiority design
• Compare outcomes between HIV+ recipients of HIV+ donors and HIV-donors
• N = 160 (80 in each arm)

Program Officer: Jonah Odim, MD PhD
Project Manager: Natasha Watson, MSN

NIH U01 Study: HIV+ deceased donor kidney transplant in the US: R34AI23023, U01AI134591

Trial Design

HIV-to-HIV Solid Organ Transplantation in the US: R34AI23023, U01AI134591

New York, New York, October 20, 2017
HIV+ candidate inclusion criteria

- No active opportunistic infections
- On effective ART with HIV RNA < 200
- Kidney CD4 > 200
- Liver CD4 > 100
- Effective ART regimen anticipated

HIV+ candidate inclusion criteria

- Standard clinical criteria for transplant
- HIV specific criteria
- UNOS organ offers per availability

"Natural randomization"

Trial Design

HIV+ kidney or liver transplant candidates

Standard clinical criteria for transplant
HIV specific criteria

UNOS organ offers per availability
"Natural randomization"

Trial Design
HIV+ donor inclusion criteria

- No active opportunistic infections or cancer
- Any HIV VL or CD4 count is allowed but study team must describe effective post-transplant antiretroviral regimen for the recipient
- Per study investigators’ clinical judgement

HIV- donor inclusion criteria

- Per transplant center study investigator clinical judgement/standard clinical criteria
Primary endpoint
• Time to composite event of major transplant and HIV related complications
• Death, graft failure, rejection, AIDS, virologic failure

Secondary endpoints:
• Graft function
• HIV-associated renal disease
• Surgical complications
• Donor specific antibodies

Other endpoints:
• HIV viral load
• CD4 counts
• HIV superinfection
• Non AIDS infections
• Post-transplant malignancies

Conclusions
• Survival benefit of transplant for HIV+ individuals with end stage organ disease
• Consider waiting to treat HCV until post transplant in some individuals
• Optimize ART (avoid strong CYP3A4 inhibitors)
• HIV+ donors may expand donor options