Cancer and end stage organ disease in HIV-infected individuals

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Johns Hopkins University School of Medicine
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Disclosures

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Gilead, Bristol Meyers Squibb

Advisory Board
Gilead

Off-label use of maraviroc
Outline

Part I: “Cancer”
  • Hematologic malignancies and HIV

Part 2: “End stage organ disease”
  • End stage liver and kidney disease
Part 1: Hematologic cancer

1. Epidemiology of heme malignancies in HIV

2. Treatment

3. Complications

4. Antiretroviral therapy (ART)
   – If? When? What?
Part 1: Hematologic cancer

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   – If? When? What?
HIV and hematologic malignancy

- Cancer accounts for 25-35% of HIV-related deaths
HIV and hematologic malignancy

• Cancer accounts for 25-35% of HIV-related deaths

• Death due to lymphoma is the most frequent cancer-related death in HIV-infected individuals
HIV and hematologic malignancy

• Cancer accounts for 25-35% of HIV-related deaths

• Death due to lymphoma is the most frequent cancer-related death in HIV-infected individuals

AIDS defining

• Non Hodgkin lymphoma
  - Diffuse large B cell
  - Primary CNS
  - Burkitt lymphoma

Non AIDS defining

• Hodgkin lymphoma
• Acute leukemia
• Multiple myeloma
Changing distribution of lymphoma types

- Hodgkin lymphoma increasing overall
- Burkitt accounting for larger proportion of NHL

Part 1: Hematologic cancer

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   – If? When? What?
Pre-ART: Palliative treatment

# Prospective trials of autoSCT

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients</th>
<th>Survival</th>
<th>Mortality related to SCT</th>
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<tbody>
<tr>
<td>Re 2003</td>
<td>16</td>
<td>60%</td>
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<tr>
<td>Krishnan 2005</td>
<td>20</td>
<td>85%</td>
<td>5%</td>
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<tr>
<td>Serrano 2005</td>
<td>11</td>
<td>64%</td>
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<tr>
<td>Spitzer 2008</td>
<td>20</td>
<td>74%</td>
<td>5%</td>
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</table>


AlloSCT series N = 23

Overall survival: 30%
After 1996 (ART): 61%

AlloSCT case reports N = 56

With ART (N=17)
Overall survival: > 50%

Part 1: Hematologic cancer

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   – If? When? What?
AutoSCT: Case control HIV+ vs HIV-
**Table 2. Causes of death for HIV-Ly and Control-Ly cohorts**

<table>
<thead>
<tr>
<th>Death events</th>
<th>HIV-Ly cohort</th>
<th>Control-Ly cohort</th>
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<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
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<tr>
<td>Relapse/progression</td>
<td>19</td>
<td>36</td>
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<tr>
<td>Secondary malignancy</td>
<td>1</td>
<td>5</td>
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<tr>
<td><strong>Infectious-related (&lt; 4 mo</strong></td>
<td>3</td>
<td>16</td>
</tr>
<tr>
<td><strong>after ASCT)</strong></td>
<td></td>
<td></td>
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<tr>
<td>Non–ASCT-related late infection</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Other</td>
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<td>0</td>
</tr>
<tr>
<td>Unknown</td>
<td>1</td>
<td>5</td>
</tr>
</tbody>
</table>
AutoSCT: Case control HIV+ vs HIV-

Overall survival

HIV+ 61.5%
HIV- 70%

P = NS

Part 1: Hematologic cancer

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4. Antiretroviral therapy (ART)
   – If? When? What?
Challenges of ART during SCT

• Drug-drug interactions
  – Cytochrome P450 inhibitors/inducers
Challenges of ART during SCT

• Drug-drug interactions
  – Cytochrome P450 inhibitors/inducers

• Organ toxicity
  – renal failure
  – liver failure
Challenges of ART during SCT

• Drug-drug interactions
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• Organ toxicity
  – renal failure
  – liver failure

• Intolerance of oral medications
  – nausea, vomiting
  – mucositis
Benefits of ART?

Mortality benefit

– Pre ART survival
Benefits of ART?

Mortality benefit
- Pre ART survival
- 35% increase in mortality per exposure to 1 log viremia

Benefits of ART?

Mortality benefit
– Pre ART survival
– 35% increase in mortality per exposure to 1 log viremia

Avoid acute retroviral syndrome with infection of new donor immune system

ART: Drug-drug interactions

**NRTIs**
- Abacavir
- Didanosine
- Emtricitabine
- Lamivudine
- Stavudine
- Tenofovir
- Zidovudine

**NNRTIs**
- Efavirenz
- Etravirine
- Nevirapine
- Rilpivirine

**PIs**
- Atazanavir
- Darunavir
- Indinavir
- Lopinavir
- Nelfinavir
- Saquinavir
- Tipranavir

**InSTIs**
- Dolutegravir
- Elvitegravir
- Raltegravir

**Anti-CCR5**
- Maraviroc

**Fusion inh**
- Enfuvirtide

**Pharmacoenhancers**
- Ritonavir
- Cobicistat
ART: Drug-drug interactions

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Strong CYP3A4 inhibitors/inducers

Conditioning chemotherapy
Cyclophosphamide

Graft versus host disease prophylaxis
Calcineurin inhibitors (CNIs)

Ritonavir $\rightarrow$ Tacrolimus $\rightarrow$ Requires infrequent, low doses of CNIs
ART: overlapping toxicities

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Neuropathy
Renal toxicity
Bone marrow suppression
ART: absorption issues, food/acidic pH

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<th>PIs</th>
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<td>Emtricitabine</td>
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**Pharmacoenhancers**
- Ritonavir
- Cobicistat
ART: least drug-drug interactions

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ART: unique benefits in SCT?

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**Pharmacoenhancers**
- Ritonavir
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Part 1: Conclusions

1. Hematologic malignancies account for the most cancer related deaths in HIV infection

2. Treatment no different standard of care

3. Complications more infections?

4. Antiretroviral therapy (ART)
   – If? When? What? Yes, soon, avoid ritonavir
Part 2: End stage liver and kidney disease
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• Causes, prevalence, and management of end stage kidney and liver disease

• Solid organ transplantation and outcomes

• Hepatitis C treatment
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Chronic kidney disease in HIV infection

• 5-10% prevalence in N America/Europe

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• HIV-associated nephropathy
• Hepatitis B/C associated nephropathy
• Antiretroviral toxicity – tenofovir, atazanavir

Chronic kidney disease in HIV infection

- 5-10% prevalence in N America/Europe
- HIV-associated nephropathy
- Hepatitis B/C associated nephropathy
- Antiretroviral toxicity – tenofovir, atazanavir
- Hypertension, diabetes, hyperlipidemia

Increasing numbers of HIV+ patients on dialysis

- 14 fold increase in prevalent HIV+ ESRD cases between 1999-2010 based on Medicare claims

HIV-positive patients
- Younger
- Hepatitis C (HCV)
- Less diabetes
Management of CKD/ESRD in HIV

Clinical Practice Guideline for the Management of Chronic Kidney Disease in Patients Infected With HIV: 2014 Update by the HIV Medicine Association of the Infectious Diseases Society of America

Gregory M. Lucas,1 Michael J. Ross,2 Peter G. Stock,3 Michael G. Shlipak,4 Christina M. Wyatt,2 Samir K. Gupta,5 Mohamed G. Atta,1 Kara K. Wools-Kaloustian,5 Paul A. Pham,1 Leslie A. Bruggeman,6 Jeffrey L. Lennox,7 Patricio E. Ray,8 and Robert C. Kalayjian6

1Johns Hopkins School of Medicine, Baltimore, Maryland; 2Icahn School of Medicine at Mount Sinai, New York, New York; 3University of California, San Francisco, and 4San Francisco Veteran Affairs Medical Center, California; 5Indiana University School of Medicine, Indianapolis; 6MetroHealth Medical Center, Case Western Reserve University, Cleveland, Ohio; 7Emory University School of Medicine, Atlanta, Georgia; and 8Children’s National Medical Center, Washington D.C.
Recommendations

• Use antiretroviral therapy (strong, moderate)

• Avoid tenofovir if GFR is < 60 (strong, low)

• Angiotensin receptor blockers if proteinuria or HIV-AN (strong, high)

• Use statins (strong, high)
HIV+ patients have a lower survival on hemodialysis

Part 2: End stage liver and kidney disease

- Causes, prevalence, and management of end stage kidney and liver disease
- Solid organ transplantation and outcomes
- Hepatitis C treatment
VII. What Is the Role of Kidney Transplantation in Patients Infected With HIV and ESRD or Imminent ESRD?

Recommendations

18. We recommend that HIV providers assess patients with HIV and ESRD or imminent ESRD for the possibility of kidney transplantation, considering history of opportunistic conditions, comorbidities, current immune status, and virologic control of HIV with ART (strong, moderate).

19. We recommend dose adjustment and pharmacologic monitoring of immunosuppressant drugs in patients infected with HIV after kidney transplantation to account for pharmacologic interactions with antiretroviral drugs. When feasible, ART should be selected that minimizes interactions with immunosuppressant drugs (strong, moderate).
Transplant studies

Outcomes of Kidney Transplantation in HIV-Infected Recipients

Peter G. Stock, M.D., Ph.D., Burc Barin, M.S., Barbara Murphy, M.D.,
Douglas Hanto, M.D., Ph.D., Jorge M. Diego, M.D., Jimmy Light, M.D.,
Charles Davis, M.D., Emily Blumberg, M.D., David Simon, M.D., Ph.D.,
Aruna Subramanian, M.D., J. Michael Millis, M.D., G. Marshall Lyon, M.D.,
Kenneth Brayman, M.D., Doug Slakey, M.D., Ron Shapiro, M.D.,
Joseph Melancon, M.D., Jeffrey M. Jacobson, M.D., Valentina Stosor, M.D.,
Jean L. Olson, M.D., Donald M. Stablein, Ph.D., and Michelle E. Roland, M.D. for
the HIV-TR Investigators
Kidney transplant

- 150 patients
- CD4 > 200, VL < 50
- Median age 46
- 70% African American, 80% male
- 25% HIV-associated nephropathy
- 25% hypertension
- 9% diabetes
Kidney transplant – overall survival

HIV+ > 65 years
1 yr: 95% 92%
3 yr: 91% 79.5%
5 yr: 87% 64.7%

HIV better outcomes than > 65

Kidney transplant – graft survival

HIV+ > 65 years

1 yr: 90% 88%
3 yr: 77% 74%
5 yr: 65% 59%

HIV better outcomes than > 65

Kidney transplant – graft rejection

HIV+ > 65 years
1 yr: 31%
3 yr: 38%
5 yr: 42%

3 fold increase

Immunosuppression after transplant

**INDUCTION**

- Anti-thymocyte globulin
- IL2 receptor blocker: Basiliximab, daclizumab
Immunosuppression after transplant

**INDUCTION**
- Anti-thymocyte globulin
- IL2 receptor blocker: Basiliximab, daclizumab

**MAINTENANCE**
- Calcineurin inhibitors: cyclosporine, tacrolimus
- Mycophenolate mofetil
- Steroids
- OR
  - Sirolimus
Ritonavir-boosted protease inhibitors

Calcineurin inhibitors
cyclosporine, tacrolimus
Ritonavir-boosted protease inhibitors
Inhibit P450 enzyme system

Calcineurin inhibitors
cyclosporine, tacrolimus

Requires infrequent, low doses of immunosuppressants
Ritonavir-boosted protease inhibitors
Inhibit P450 enzyme system

Calcineurin inhibitors
cyclosporine, tacrolimus

Requires infrequent, low doses of immunosuppressants

Reason for increased graft rejection?
> 50% of patients on PIs in trials
Non-nucleoside reverse transcriptase inhibitors
Induction of P450

Calcineurin inhibitors
cyclosporine, tacrolimus

Calcineurin inhibitors
cyclosporine, tacrolimus
Antiretroviral therapy and drug interactions

- Integrase strand transfer inhibitors
- Nucleoside reverse transcriptase inhibitors
- CCR5 receptor antagonists

Calcineurin inhibitors: cyclosporine, tacrolimus
CCR5 receptor antagonists

Early report

CC chemokine receptor 5 and renal-transplant survival


Fischereder et al. Lancet. 2001
Beneficial antiretroviral therapy?

Early report

**CC chemokine receptor 5 and renal-transplant survival**


Blockade of Lymphocyte Chemotaxis in Visceral Graft-versus-Host Disease


Fischereder et al. Lancet. 2001
Reshef et al. NEJM. 2013
Opportunistic infections and transplant

Pre-transplant
Prior history of an OI
N = 52
• 30 PCP
• 8 CMV
• 7 MAC
• 3 KS

Opportunistic infections and transplant

Pre-transplant
Prior history of an OI
N = 52
• 30 PCP
• 8 CMV
• 7 MAC
• 3 KS

Post-transplant
N = 13
• 4 KS
• 3 PCP
• 1 cryptosporidiosis
• 6 candida (esophagitis 5, bronchial 1)

## Opportunistic infections and transplant

### Pre-transplant

Prior history of an OI

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>30 PCP</td>
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<tr>
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<td>7 MAC</td>
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</tbody>
</table>

### Post-transplant

N = 13

| 4 KS |
| 3 PCP |
| 1 cryptosporidiosis |
| 6 candida |

No recurrences in patients with OI history

No survival difference with OI history

HIV+ candidate selection criteria

Kidney

- CD4 > 200
- HIV RNA “undetectable”
- No active OIs
- No lymphoma
Liver disease in HIV infection

- Hepatitis C
- Hepatitis B
- Alcohol
- Non-alcoholic steatohepatitis
Liver related deaths increasing

DAD study group. AIDS. 2010.
HIV and liver transplant: HCV/HIV

- HCV is the #1 reason for liver transplant in US
HIV and liver transplant: HCV/HIV

• HCV is the #1 reason for liver transplant in US

• Even if our efforts at diagnosis and treatment are 100% successful, in 2030 the need for liver transplant is predicted to outstrip the supply by > 3 fold Rein DB et al. Dig Liver Dis. 2011;43:66-72.
HIV and liver transplant: HCV/HIV

• HCV is the #1 reason for liver transplant in US

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• Approximately 2% of all individuals listed for liver transplant are HIV+  OPTN data
Liver transplant studies HIV/HCV

Outcomes of Liver Transplant Recipients with Hepatitis C and Human Immunodeficiency Virus Coinfection


for the Solid Organ Transplantation in HIV: Multi-Site Study Investigators

1University of California San Francisco, San Francisco, CA; 2Mount Sinai School of Medicine, New York, NY; 3New York Presbyterian Hospital-Columbia, New York, NY; 4Beth Israel Deaconess Medical Center, Boston, MA; 5Cedars-Sinai Medical Center, Los Angeles, CA; 6University of Pittsburgh, Pittsburgh, PA; 7EMMES Corporation, Rockville, MD; 8Rush University, Chicago, IL; 9University of Pennsylvania, Philadelphia, PA; 10Georgetown Medical Center, Washington, DC; 11Northwestern University, Chicago, IL; 12University of Miami, Miami, FL; 13Cleveland Clinic, Cleveland, OH; 14University of Cincinnati, Cincinnati, OH; 15Johns Hopkins University, Baltimore, MD; 16University of Chicago, Chicago, IL; 17Tulane University, New Orleans, LA; 18University of Virginia, Charlottesville, VA; and 19National Institute of Allergy and Infectious Diseases, Bethesda, MD

Outcome of HCV/HIV-Coinfected Liver Transplant Recipients: A Prospective and Multicenter Cohort Study

Liver transplant - overall survival

**Significantly lower**

**Spanish study**
- HIV+/HCV+: 54%
- HCV+: 71%

5 yr: 54%  


**US study**
- HIV+/HCV+: 60%
- HCV+: 79%

3 yr: 60%  

Selected lower risk individuals HCV+/HIV+

HCV negative donor
BMI > 21
No combined kidney transplant

3 year survival

HIV+/HCV+ 60%  low 72%  high 29%  HCV+ 79%

Selected lower risk individuals HCV+/HIV+

Favorable HCV genotype
Lower MELD
Experienced hospital

5 year survival

<table>
<thead>
<tr>
<th></th>
<th>low</th>
<th>high</th>
<th>HCV+</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV+/HCV+</td>
<td>69%</td>
<td>17%</td>
<td>71%</td>
</tr>
</tbody>
</table>

HIV+ liver transplant selection criteria

Lever

- CD4 > 100
- Predicted ability to control viremia
- No active OIs
- No lymphoma
HIV+ liver transplant selection criteria

Liver

- CD4 > 100
- Predicted ability to control viremia
- No active OIs
- No lymphoma

- Experienced center
- Consider referral with lower MELD
- What about treating hepatitis C?
Part 2: End stage liver and kidney disease

- Causes, prevalence, and management of end stage kidney and liver disease
- Solid organ transplantation and outcomes
- Hepatitis C treatment
HCV recurrence after liver transplant

• 100% re-infection of new liver if detectable HCV RNA at the time of transplant

• 10–50% of patients with recurrent infection progress to cirrhosis within 5 years\(^1\)

• Once cirrhosis is established, the probability of liver graft failure is 42% within 12 months\(^2\)

HCV treatment: pre or post transplant?

• Challenges
  – Drug delivery: cirrhotic liver
  – Renal function: drugs not dosed for CrCl < 30
  – Timing of transplant – predictable?
  – Organ supply – HCV+ donors – kidneys in particular
HCV treatment as bridge to transplant

• Compensated cirrhotics with hepatocellular carcinoma
  – Any HCV genotype
  – Childs Pugh Turcotte Class A
• Sofosbuvir + weight based ribavirin
  – Duration: 48w, or until time of transplant
• Primary endpoint: pTVR 12
• No HIV infected individuals

Patients

SOF + RBV (N=61)

- On Treatment (n=1)
  - HCV RNA >LLOQ at Transplant (n=3)
    - On-tx failure (n=1), relapse (n=2)
- Post Treatment (n=4)
- Liver Transplantation (n=44)
- D/C Study Prior to OLTx (n=12)

HCV RNA <LLOQ at Transplant (n=41)

Results: post-transplant SVR

10 relapses after transplant

Days with HCV RNA Continuously TND prior to Liver Transplant

- **No recurrence (n=28):** Median days TND = 95
- **Recurrence (n=10):** Median days TND = 5.5

*p < 0.001

Curry MP et al. 2013 AASLD Annual Meeting. Abstract 213
Days undetectable HCV RNA prior to transplant

- No relapses if 90 days of undetectable virus
- 1/10 relapsed with 30 days negative

Pre-transplant – patient types

Can you avoid need for transplantation?

Clinical status
• Low MELD < 15
• High MELD > 15

Can you effectively prevent infection of the new liver?

Predictable time of transplant
• Hepatocellular carcinoma
• Living donor recipients
Part 2: Conclusions

• Increasing prevalence of ESRD and ESLD

• Good outcomes of kidney and liver transplant
  – Higher rates of rejection
  – Drug-drug interactions: avoid ritonavir

• HCV treatment – new era
Acknowledgements

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