Updates in Transplantation 2016

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Disclosure

- The program chair and presenters for this continuing education activity have reported no relevant financial relationships.
Objectives

- Summarize the major updates in transplantation in the past year, including the rising prevalence of transplantation in HIV+ recipients

- Assess the advantages and limitations of HIV pharmacotherapy in the pre-, peri-, and post-transplant settings

- Evaluate immunosuppression and opportunistic infection prophylaxis regimens specific to the HIV+ transplant recipient

- Create an effective post-transplant immunosuppressive regimen for an HIV+ transplant recipient
Introduction of HAART in 1996

Development of ESRD & ESLD in HIV Patients

- Increased life expectancy of patients with HIV
- Development of long-term complications
  - Risk of end stage renal disease (ESRD)
    - HIV associated nephropathy
    - ART related kidney damage
  - Risk of end stage liver disease (ESLD)
    - Co-infection with HCV or HBV

Organ Supply & Demand

A Long Wait for a Kidney
Since 1990, the number of people on the waiting list for a kidney transplant has grown sharply, while the number of transplants has increased only slightly.

Patients on waiting list

Transplants
Living transplants
Deaths on the waiting list

Source: The Organ Procurement and Transplantation Network
The Wall Street Journal

HIV Organ Policy Equity (HOPE) Act

- Will allow for research into transplanting organs from HIV-positive donors into HIV-positive recipients
- Enacted on November 21, 2013
- In 2016, first HIV-to-HIV kidney and liver transplant in US was performed

Image courtesy of www.livingbank.com
Updates in Transplantation 2016

Janessa M. Smith, Pharm.D., BCPS
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Objectives

- Assess advantages and limitations of HIV pharmacotherapy in the pre-, peri-, and post-transplant setting
Who Should Get Antiretroviral Therapy?

- DHHS Guidelines for the Use of Antiretroviral Agents in HIV-1 Infected Adults and Adolescents recommend initiating antiretroviral therapy (ART) in **ALL** HIV-infected patients, regardless of CD4 cell count (AI)

- Initiation at any CD4 cell count may delay or prevent HIV-associated morbidity (e.g., HIV-associated nephropathy (HIVAN), liver disease, cardiovascular disease, neurologic complications and malignancies), mortality and transmission

What to Start

- Three drugs from at least 2 classes (i.e., two mechanisms of action)
  - NRTI – nucleos(t)ide reverse transcriptase inhibitor
  - NNRTI – non-nucleoside reverse transcriptase inhibitor
  - PI – protease inhibitor
  - INSTI – integrase strand transfer inhibitor
  - EI – entry inhibitor
- Usually 2 from the NRTI class and a 3rd agent from NNRTI, PI, INSTI or EI class
# What to Start

<table>
<thead>
<tr>
<th>NRTI</th>
<th>NNRTI</th>
<th>PI</th>
<th>INSTI</th>
<th>EI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abacavir</td>
<td>Efavirenz</td>
<td>Atazanavir</td>
<td>Dolutegravir</td>
<td>Enfuviritide</td>
</tr>
<tr>
<td>Didanosine</td>
<td>Etravirine</td>
<td>Darunavir</td>
<td>Elvitegravir</td>
<td>Maraviroc</td>
</tr>
<tr>
<td>Emtricitabine</td>
<td>Nevirapine</td>
<td>Indinavir</td>
<td></td>
<td></td>
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<tr>
<td>Lamivudine</td>
<td>Rilpivirine</td>
<td>Lopinavir</td>
<td>Raltegravir</td>
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<tr>
<td>Stavudine</td>
<td></td>
<td>Saquinavir</td>
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<tr>
<td>Tenofovir</td>
<td></td>
<td>Tipranavir</td>
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</tr>
<tr>
<td>Zidovudine</td>
<td></td>
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</tr>
</tbody>
</table>
DHHS Recommended Regimens

- **INSTI-based Regimen**
  - Dolutegravir/Abacavir/Lamivudine
  - Dolutegravir PLUS Tenofovir/Emtricitabine
  - Elvitegravir/cobicistat/Tenofovir/Emtricitabine
  - Raltegravir PLUS Tenofovir/Emtricitabine

- **PI-based Regimen**
  - Darunavir PLUS ritonavir PLUS Tenofovir/Emtricitabine

Considerations When Selecting ART for Transplant Patients

**Pre-transplant**
- Comorbidities
- HIV resistance
- HIV viral load, CD4 cell count

**Peri-transplant**
- Rapidly changing renal function
- Oral intake

**Post-transplant**
- Pill burden
- Dosing frequency
- Drug interactions
- Graft effects
Comorbidity Considerations

- Cardiovascular disease
  - Abacavir associated increased risk of myocardial infarction
  - PI-based therapy associated with dyslipidemia
- Co-infection with hepatitis B
  - Lamivudine and tenofovir can be used to treat HIV and HBV co-infected patients
- Co-infection with hepatitis C
  - Drug interactions

- Chronic kidney disease
  - Avoid tenofovir disoproxil fumarate (CrCl <70 mL/min)
  - Avoid tenofovir alafenamide (CrCl <30 mL/min)
- Severe liver disease
  - Avoid abacavir
  - Use PI with caution (dose adjustments, some contraindicated)
Immediate Peri-transplant Considerations

- **Kidney transplant**
  - NRTIs (except abacavir) require renal dose adjustment and dose should be modified during peri-transplant period as renal function improves.
  - Avoid single tablet regimens and NRTI fixed-dose combination products until renal function improves/stabilizes.

- **Liver transplant**
  - Avoid ART that requires high calorie intake (e.g., rilpivirine) or acid environment for absorption (e.g., atazanavir, rilpivirine).
Pill Burden

- Pill burden
  - Single-tablet regimens preferred
  - Associated with increased adherence (OR 1.98, p <0.001), virologic suppression (OR 1.21, p <0.001) and reduced hospitalizations (HR 0.69, p <0.001) as compared to multiple-tablet regimens (based on prescription data)

- Dosing frequency
  - Once-daily dosing preferred
  - Associated with increased adherence compared with twice-daily dosing in randomized controlled trials

# Combination Products

## NRTI Combinations

<table>
<thead>
<tr>
<th>Product</th>
<th>Active Ingredients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Combivir®</td>
<td>Lamivudine/zidovudine</td>
</tr>
<tr>
<td>Descovy®</td>
<td>Emtricitabine/tenofovir alafenamide</td>
</tr>
<tr>
<td>Epzicom®</td>
<td>Abacavir/lamivudine</td>
</tr>
<tr>
<td>Trizivir®</td>
<td>Abacavir/lamivudine/zidovudine</td>
</tr>
<tr>
<td>Truvada®</td>
<td>Emtricitabine/tenofovir disoproxil fumarate</td>
</tr>
</tbody>
</table>

## PI/Booster Combinations

<table>
<thead>
<tr>
<th>Product</th>
<th>Active Ingredients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evotaz®</td>
<td>Atazanavir/cobicistat</td>
</tr>
<tr>
<td>Kaletra®</td>
<td>Lopinavir/ritonavir</td>
</tr>
<tr>
<td>Prezcobix®</td>
<td>Darunavir/cobicistat</td>
</tr>
</tbody>
</table>

## Single Tablet Regimens

<table>
<thead>
<tr>
<th>Product</th>
<th>Active Ingredients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atripla®</td>
<td>Efavirenz/emtricitabine/tenofovir disoproxil fumarate</td>
</tr>
<tr>
<td>Complera®</td>
<td>Rilpivirine/emtricitabine/tenofovir disoproxil fumarate</td>
</tr>
<tr>
<td>Genvoya®</td>
<td>Elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide</td>
</tr>
<tr>
<td>Odefsey®</td>
<td>Rilpivirine/emtricitabine/tenofovir alafenamide</td>
</tr>
<tr>
<td>Stribild®</td>
<td>Elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate</td>
</tr>
<tr>
<td>Triumeq®</td>
<td>Dolutegravir/abacavir/lamivudine</td>
</tr>
</tbody>
</table>
Drug Interactions with ART

- **Absorption**
  - E.g. chelation, gastric acid, P-gp
- **Distribution**
  - E.g. competition for protein binding
- **Metabolism**
  - E.g. CYP450 enzymes
- **Elimination**
  - E.g. inhibition of renal clearance
Managing Drug Interactions

Risks of Adverse Effects with DDI

1. Review available pharmacokinetic and clinical data
2. Assess clinical significance
3. Identify potential alternatives
4. If no alternatives, consider monitoring parameters

Benefit of Interacting Drug
Overview Drug Interaction Concerns

- Calcineurin inhibitors (CNI) and mTOR inhibitors with PI, ritonavir, cobicistat and NNRTI
- INSTI with oral electrolyte repletion
- Acid suppression with atazanavir and rilpivirine
CNI and ART

- Cyclosporine and tacrolimus are major substrates of CYP3A4 and P-gp
- Interactions with PI, ritonavir, or cobicistat (inhibitors of CYP3A4) can result in increased exposure of CNI and increased toxicity
- Interactions with NNRTIs (inducers of CYP3A4) may result in decreased exposure of CNI and loss of efficacy
  - Note: rilpivirine is not an inducer of 3A4
Management of CNI with ART

- **Tacrolimus**
  - Ritonavir-boosted therapy can result in a 5- to 10-fold increase in AUC and >10-fold increase in half-life
  - Cobicistat is expected to have the same effect as ritonavir
  - Variability amongst PI and interpatient variability exists
  - Consider initial dose of 0.5-1 mg *once weekly* with close monitoring and adjustments based on tacrolimus levels

- **Cyclosporine**
  - PI, ritonavir, cobicistat can result in 5-fold increase in trough concentrations and prolong elimination half-life by 2-fold
  - Consider reducing initial daily dose by 80% with close monitoring of cyclosporine A levels

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Management of CNI with NNRTI Therapy

- Efavirenz, etravirine and nevirapine are moderate inducers of 3A4 and may result in significant reductions of CNI concentrations
- Interaction not well studied – if co-administration required close monitoring of trough concentrations should guide dose adjustments
  - Muller *et al.* reported a median tacrolimus dose was 8.5 mg Q12H in patients on efavirenz or nevirapine
  - Frassetto *et al.* reported similar doses of cyclosporine with efavirenz and nevirapine as non-HIV-infected patients
- Full induction (or de-induction) of CYP3A4 enzymes may take up to 2-4 weeks when starting (or stopping) NNRTI therapy

m-TOR Inhibitors with ART

- Sirolimus and everolimus are major substrates of CYP3A4 and P-gp
- Interactions with PI, ritonavir and cobicistat may lead to significant increases in AUC
  - Jain et al. reported 60% increase in AUC and 9-fold increase in trough levels with nelfinavir co-administration
  - Barau et al. reported once weekly sirolimus dosing (1.5 mg) to maintain sirolimus troughs of 8-10 ng/mL
- Interaction with NNRTI not well studied – if co-administration required close monitoring of trough concentrations should guide dose adjustments
  - Full induction/de-induction of CYP3A4 enzymes may take up to 2-4 weeks when starting or stopping NNRTI therapy

INSTI and Oral Electrolyte Replacement

- INSTI form a metal-drug complex with polyvalent cations resulting in impaired oral absorption
  - Al, Mg, Ca-containing antacids (e.g., Maalox, Tums), supplements (MVI, PhosLo) or Fe products
  - Only applies to oral products – IV electrolytes are not an issue
- Degree of interaction and management varies with INSTI
### Raltegravir and Oral Electrolyte Replacement

- **Avoid** Mg-containing products with twice daily raltegravir
- **CaCO₃**: **Use with CAUTION**
  - Manufacturer states that the interaction did not lead to clinically meaningful changes to raltegravir concentrations
  - Case report of virologic failure with reduced raltegravir serum levels in a patient on CaCO₃ and raltegravir

<table>
<thead>
<tr>
<th></th>
<th>Simultaneous</th>
<th>2 hr before</th>
<th>2 hr after</th>
<th>6 hr before</th>
<th>6 hr after</th>
</tr>
</thead>
<tbody>
<tr>
<td>RAL + Mg-Al</td>
<td>Cmax: ↓46%</td>
<td>Cmax: ↓51%</td>
<td>Cmax: ↓22%</td>
<td>Cmax: ↓10%</td>
<td>Cmax: ↓10%</td>
</tr>
<tr>
<td></td>
<td>AUC: ↓49%</td>
<td>AUC: ↓51%</td>
<td>AUC: ↓30%</td>
<td>AUC: ↓13%</td>
<td>AUC: ↓11%</td>
</tr>
<tr>
<td></td>
<td>Cmin: ↓63%</td>
<td>Cmin: ↓56%</td>
<td>Cmin: ↓57%</td>
<td>Cmin: ↓50%</td>
<td>Cmin: ↓49%</td>
</tr>
<tr>
<td>RAL + CaCO₃ (3 g)</td>
<td>Cmax: ↓52%</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>AUC: ↓55%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cmin: ↓32%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Roberts JL. Pharmacotherapy. 2011;31(10):298e-302e.
Dolutegravir and Oral Electrolyte Replacement

- **Space** Mg-Al-containing products
- **CaCO₃**: Use with CAUTION
  - Give simultaneously with food OR space administration
- Space administration: 2 hr before or 6 hr after dolutegravir

<table>
<thead>
<tr>
<th></th>
<th>Simultaneous</th>
<th>2 hr after/Fed*</th>
<th>Simultaneous</th>
<th>2 hr after/Fed</th>
</tr>
</thead>
<tbody>
<tr>
<td>DTG + Mg-Al</td>
<td>Cmax: ↓72% AUC: ↓74% Cmin: ↓74%</td>
<td>Cmax: ↓18% AUC: ↓26% Cmin: ↓30%</td>
<td>DTG + FeSO₄ (324 mg)</td>
<td>Cmax: ↓57% AUC: ↓54% Cmin: ↓56%</td>
</tr>
<tr>
<td>DTG + CaCO₃ (1.2 g)</td>
<td>Cmax: ↓37% AUC: ↓39% Cmin: ↓39%</td>
<td>Cmax: no effect AUC: no effect Cmin: no effect</td>
<td>DTG + MVI</td>
<td>Cmax: ↓35% AUC: ↓37% Cmin: ↓32%</td>
</tr>
</tbody>
</table>

*Mg-Al not studied under fed conditions

Elvitegravir and Oral Electrolyte Replacement

- Data on the effect of polyvalent cations on elvitegravir concentrations is limited
  - No data on simultaneous administration
  - Spacing by 2 and 4 hours did not affect elvitegravir

- Manufacturer recommends to space antacids (Mg-Al or CaCO$_3$) by 2 hours

Acid Suppression

- Not limited to transplant patients

- Atazanavir and rilpivirine are more soluble and best absorbed at lower gastric pH

Management

- Atazanavir: Space administration of all acid-suppressing medications (e.g., PPI, H2RA, antacids)
- Rilpivirine: **avoid** PPI, space administration of other acid-suppressing medications (e.g., H2RA, antacids)
## Optimal ART Regimens

<table>
<thead>
<tr>
<th>NRTI</th>
<th>NNRTI</th>
<th>PI</th>
<th>INSTI</th>
<th>EI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abacavir</td>
<td>Efavirenz</td>
<td>Atazanavir</td>
<td>Dolutegravir</td>
<td>Enfuviritide</td>
</tr>
<tr>
<td>Didanosine</td>
<td>Etravirine</td>
<td>Darunavir</td>
<td>Elvitegravir</td>
<td>Maraviroc</td>
</tr>
<tr>
<td>Emtricitabine</td>
<td>Nevirapine</td>
<td>Indinavir</td>
<td>Raltegravir</td>
<td></td>
</tr>
<tr>
<td>Lamivudine</td>
<td>Rilpivirine</td>
<td>Lopinavir</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stavudine</td>
<td></td>
<td>Saquinavir</td>
<td></td>
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</tr>
<tr>
<td>Tenofovir</td>
<td></td>
<td>Tipranavir</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tenofovir</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zidovudine</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Optimal ART Regimens

<table>
<thead>
<tr>
<th>NRTI</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Abacavir</strong></td>
<td>Lamivudine or emtricitabine preferred</td>
</tr>
<tr>
<td>Didanosine</td>
<td>Abacavir if HLA-B5701 negative and low cardiac risk</td>
</tr>
<tr>
<td>Emtricitabine</td>
<td>Tenofovir alafenamide preferred over tenofovir</td>
</tr>
<tr>
<td>Lamivudine</td>
<td>disoproxil fumarate given less renal and bone toxicity</td>
</tr>
<tr>
<td>Stavudine</td>
<td>Tenofovir/emtricitabine NRTI backbone preferred in</td>
</tr>
<tr>
<td>Tenofovir</td>
<td>patients co-infected with hepatitis B virus</td>
</tr>
<tr>
<td>Zidovudine</td>
<td></td>
</tr>
</tbody>
</table>
# Optimal ART Regimens

<table>
<thead>
<tr>
<th>NNRTI</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Efavirenz</td>
<td>• Avoid efavirenz, nevirapine, etravirine given significant and complicated drug interactions with CNI</td>
</tr>
<tr>
<td>Etravirine</td>
<td>• Avoid rilpivirine in patients that require acid suppression or unable to intake at least 500 calories with each dose</td>
</tr>
<tr>
<td>Nevirapine</td>
<td></td>
</tr>
<tr>
<td>Rilpivirine</td>
<td></td>
</tr>
</tbody>
</table>
# Optimal ART Regimens

<table>
<thead>
<tr>
<th>PI</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Atazanavir</td>
<td>• Avoid PI-based therapy given significant and complicated drug interactions with CNI, m-TOR inhibitors</td>
</tr>
<tr>
<td>Darunavir</td>
<td></td>
</tr>
<tr>
<td>Fosamprenavir</td>
<td></td>
</tr>
<tr>
<td>Indinavir</td>
<td></td>
</tr>
<tr>
<td>Lopinavir</td>
<td></td>
</tr>
<tr>
<td>Nelfinavir</td>
<td></td>
</tr>
<tr>
<td>Saquinavir</td>
<td></td>
</tr>
<tr>
<td>Tipranavir</td>
<td></td>
</tr>
</tbody>
</table>
# Optimal ART Regimens

<table>
<thead>
<tr>
<th>INSTI</th>
<th>Dolutegravir</th>
<th>Elvitegravir</th>
<th>Raltegravir</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• Dolutegravir preferred</td>
<td></td>
<td>• Avoid raltegravir in patients that require oral magnesium for repletion</td>
</tr>
<tr>
<td></td>
<td>• Avoid elvitegravir since requires cobicistat or ritonavir for PK enhancement</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## Optimal ART Regimens

| EI |  
|---|---|
| **Enfuviritide**  | • Maraviroc if R5 trophic virus – potential additive benefit of graft protection  
**Maraviroc** |
Key Takeaways

- Optimal management strategy is to avoid PI-, EVG-, and NNRTI-based therapy when possible
  - If co-administration is required, closely monitor CNI and m-TOR serum levels initially and when changing ART
- Many other drug interactions with ART to consider outside immunosuppressants
- Dolutegravir with an NRTI-backbone is preferred
Updates in Transplantation 2016

Erin H. Ticehurst, Pharm.D.
Clinical Pharmacy Specialist, Liver Transplantation
Hospital of the University of Pennsylvania
Rejection is more common in HIV+ kidney transplant recipients than HIV- recipients

A  TRUE

B  FALSE
## KTX Key Trial

<table>
<thead>
<tr>
<th>Methods</th>
<th>Patient survival</th>
<th>Graft survival</th>
<th>Rejection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prospective, multi-center</td>
<td>1 year 94.6±2%</td>
<td>90.4%</td>
<td>31%</td>
</tr>
<tr>
<td></td>
<td>3 years 88.2±3.8%</td>
<td>73.7%</td>
<td>41%</td>
</tr>
</tbody>
</table>

Only half of rejection episodes responded to steroids

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Stock PG et al. NEJM 2010;363:2004-14
Objectives

- Evaluate immunosuppression and opportunistic infection prophylaxis regimens specific to the HIV+ transplant recipient
- Create an effective post-transplant immunosuppressive regimen for an HIV+ transplant recipient
Immunosuppression Considerations

Regimen

- Efficacy
- HIV impact
- Side effects
## KTX Induction

<table>
<thead>
<tr>
<th>Methods</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scientific Registry of Transplant Recipients</td>
</tr>
<tr>
<td>KTX performed 2000 – 2014 (n=830)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Induction reduced hospital stay and lowered rates of delayed graft function as well as graft loss</td>
</tr>
<tr>
<td>Anti-thymocyte globulin associated with lowered rates of acute rejection (wRR 0.59, 95% CI 0.35-0.99) compared to other strategies</td>
</tr>
<tr>
<td>Induction did not increase infection rate</td>
</tr>
</tbody>
</table>

# KTX Anti-Thymocyte Globulin Induction

| Methods                      | Single center  
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>KTX performed 2006 – 2013 and received anti-thymocyte globulin (n=38)</td>
</tr>
<tr>
<td></td>
<td>Baseline CD4+ count &gt; 350 versus &lt; 350 cells/mm³</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Findings</th>
<th>Median follow-up 2.6 years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Increased rate of severe CD4+ lymphopenia &amp; higher serious infection rate in patients with pre-transplant CD4+ count &lt; 350 cells/mm³</td>
</tr>
</tbody>
</table>

# KTX Basiliximab Induction

<table>
<thead>
<tr>
<th>Methods</th>
<th>Multi-center</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>KTX performed 2005 – 2009 (n=27)</td>
</tr>
<tr>
<td></td>
<td>Basiliximab</td>
</tr>
<tr>
<td></td>
<td>Cyclosporine or tacrolimus</td>
</tr>
<tr>
<td></td>
<td>Mycophenolate mofetil</td>
</tr>
<tr>
<td></td>
<td>Methylprednisolone/prednisone taper</td>
</tr>
<tr>
<td>Findings</td>
<td>Patient survival</td>
</tr>
<tr>
<td></td>
<td>1 year 100%</td>
</tr>
<tr>
<td></td>
<td>2 years 98%</td>
</tr>
<tr>
<td></td>
<td>Graft survival</td>
</tr>
<tr>
<td></td>
<td>1 year 98%</td>
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<tr>
<td></td>
<td>2 years 96%</td>
</tr>
<tr>
<td></td>
<td>15% had acute cellular rejection</td>
</tr>
</tbody>
</table>

Induction

- Induction recommended for KTX
- Unclear for OLT
- Patient-specific considerations

Maintenance

Rejection
Calcineurin Inhibitors

- Cyclosporine has theoretical anti-HIV and anti-HCV activity
- Tacrolimus preferred over cyclosporine due to lower rejection rates
- $C_0$ correlates well with AUC for tacrolimus but not for cyclosporine

Blumberg EA, Rogers CC. Am J Trans 2013;13(S4):169-78
Frassetto LA et al. Transplantation 2014;97:702-7
## KTX Calcineurin Inhibitors

<table>
<thead>
<tr>
<th>Methods</th>
<th>National observational study (UK) KTX performed 2005 – 2013 without primary graft failure (n=78)</th>
</tr>
</thead>
</table>
| Findings                                    | Acute rejection rate at 1 year (p=0.003):  
Cyclosporine 58%  
Tacrolimus 21%                                      |
Antiproliferatives

- Mycophenolate products may suppress HIV replication particularly in a NRTI regimen
- Mycophenolate products are more potent and preferred over azathioprine

Margolis DM et al. J Acquir Immune Defic Syndr 2002;31:45-9
Belatacept

- Belatacept potential advantages
  - Fewer drug-drug interactions
  - Side effect profile
KTX De Novo Belatacept

- Case report of de novo belatacept, mycophenolate mofetil and prednisone with basiliximab induction
- No rejection or graft loss within 18 months of follow-up

KTX Belatacept Conversion

- Case report
- Initial immunos were basiliximab, mycophenolate, tacrolimus and prednisone taper
- Conversation from tacrolimus at week 14 due to delayed graft function
- Dialysis was no longer indicated at 21 weeks
- One borderline rejection episode treated with prednisone boluses

Sirolimus inhibits HIV-1 progression via:
- Reducing CCR5-gene transcription
- Blocking interleukin-2 intracellular secondary messenger (mTOR)
- Up-regulating the β-chemokine macrophage inflammatory protein

Possibly reservoir-modifying activity:
- Associated with lower post-transplant HIV DNA levels
- May have anti-HHV8 activity so possible role with Kaposi’s sarcoma

Di Benedetto FD et al. Transplantation 2010;89(6):733-8
### OLT Sirolimus Conversion

<table>
<thead>
<tr>
<th>Methods</th>
<th>Single-center OLT performed 2003 - 2009 (n=14)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Initial immunos were tacrolimus (n=2) or cyclosporine (n=12) plus steroids</td>
</tr>
<tr>
<td></td>
<td>Cyclosporine was changed to sirolimus for 6 patients due to renal dysfunction or Kaposi’s sarcoma</td>
</tr>
<tr>
<td>Findings</td>
<td>Reduced HIV &amp; HCV viral load with sirolimus</td>
</tr>
</tbody>
</table>

Di Benedetto FD et al. Transplantation 2010;89(6):733-8
# KTX Early Steroid Withdrawal

<table>
<thead>
<tr>
<th>Methods</th>
<th>Single-center</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>KTX performed 2006 – 2010 (n=11)</td>
</tr>
<tr>
<td></td>
<td>9 anti-thymocyte globulin, 2 basiliximab</td>
</tr>
<tr>
<td></td>
<td>Methylprednisolone days 0-4</td>
</tr>
<tr>
<td></td>
<td>Tacrolimus</td>
</tr>
<tr>
<td></td>
<td>Mycophenolate mofetil</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Findings</th>
<th>1 year outcomes:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Acute rejection 9%</td>
</tr>
<tr>
<td></td>
<td>Patient survival 100%</td>
</tr>
<tr>
<td></td>
<td>Graft survival 91% (primary non-function)</td>
</tr>
</tbody>
</table>
## KTX Early Steroid Withdrawal

| Methods               | Single-center  
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>KTX performed 2007 – 2012 (n=13)</td>
</tr>
<tr>
<td></td>
<td>Basiliximab, methylprednisone taper x 5 days, calcineurin inhibitor, &amp; mycophenolic acid</td>
</tr>
<tr>
<td>Findings</td>
<td>61.5% patients had acute rejection with half resuming steroids</td>
</tr>
<tr>
<td></td>
<td>4 year outcomes:</td>
</tr>
<tr>
<td></td>
<td>Patient survival  100%</td>
</tr>
<tr>
<td></td>
<td>Graft survival     89%</td>
</tr>
<tr>
<td></td>
<td>eGFR 58±40 ml/min if patient had acute rejection versus 76±6 ml/min if no rejection</td>
</tr>
</tbody>
</table>

Bossini N et al. Transplant Int 2014;27:1050-9
Induction

Maintenance

- Tacrolimus-based
- More data needed to determine the role of other agents

Rejection
- Steroid boluses (low vs high)
- Maximize mycophenolate and calcineurin inhibitor
- Sirolimus
- Avoid anti-thymocyte globulin unless refractory

Fox AM, Vagefi PA, Stock PG. J Semin Liver Dis 2012;32:177-85
Opportunistic infections are more common in HIV+ kidney transplant recipients than in HIV- recipients

A TRUE
B FALSE
## OI Primary Prophylaxis Recommendations

<table>
<thead>
<tr>
<th>Infection</th>
<th>Agent of Choice</th>
<th>Criteria &amp; Duration for Primary Prophylaxis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumocystis pneumonia</td>
<td>Sulfamethoxazole/trimethoprim</td>
<td>Lifelong</td>
</tr>
<tr>
<td>Cytomegalovirus</td>
<td>Valganciclovir</td>
<td>CMV IgG+ donor or recipient. Continue x ≥ 3 months</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Infection</th>
<th>Agent of Choice</th>
<th>Criteria &amp; Duration for Primary Prophylaxis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Toxoplasma gondii</td>
<td>Sulfamethoxazole/trimethoprim</td>
<td>Toxoplasmosis IgG+ donor or IgG+ recipient with CD4+ count ≤ 200 cells/mm³</td>
</tr>
<tr>
<td>Mycobacterium avium complex</td>
<td>Azithromycin</td>
<td>CD4+ count ≤ 50-75 cells/mm³. Continue until &gt; 100 cells/mm³ x 6 months</td>
</tr>
</tbody>
</table>

# OI Primary Prophylaxis Recommendations (cont’d)

<table>
<thead>
<tr>
<th>Infection</th>
<th>Agent(s) of Choice</th>
<th>Criteria &amp; Duration for Primary Prophylaxis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Histoplasma capsulatum</td>
<td>Itraconazole</td>
<td>CD4+ count &lt; 150 cells/mm³ plus occupational or residential risk factors</td>
</tr>
<tr>
<td>Coccidioidomycosis</td>
<td>Fluconazole or itraconazole</td>
<td>IgG or IgM+ if from an endemic area when CD4+ count &lt; 250 cells/mm³. Lifelong if donor history of coccidioides</td>
</tr>
</tbody>
</table>

Key Takeaways

- More experience is needed to determine patient-specific optimal immunosuppression

- Opportunistic infection prophylaxis strategies differ from standard organ transplant protocols so close attention needs to be paid
Patient Case

JR is a 43 yo male with past medical history significant for HIV, hypertension and ESRD secondary to HIV-associated nephropathy on hemodialysis three times a week. He is being considered for a kidney transplant and presents to clinic today for antiretroviral therapy modification in preparation for transplant.

His HIV has been well controlled for the past 3 months on darunavir 800 mg once daily, ritonavir 100 mg once daily, raltegravir 400 mg twice daily and tenofovir disoproxil fumarate 300 mg once weekly. He reports missing 1-2 doses per month. His most recent CD4 436 cells/mm³ and HIV RNA <20 copies/mL. He has no HIV resistance detected.
Patient Case

Current medications:
- Nifedipine XL 90 mg once daily
- Atorvastatin 20 mg daily
- Aspirin 81 mg daily
- Cinacalcet 90 mg daily
- Sevelamer 800 mg three times daily with meals
- Darunavir 800 mg daily
- Ritonavir 100 mg daily
- Raltegravir 400 mg twice daily
- Tenofovir DF 300 mg once weekly

Labs:
- Na: 135 mEq/L
- K: 4.7 mEq/L
- Cl: 100 mEq/L
- Ca: 9.7 mg/dL
- Scr: 7.8 mg/dL
- BUN: 45 mg/dL
- Gluc: 147 mg/dL
- AST: 20 U/L
- ALT: 18 U/L
- Alk phos: 60 U/L
- T. bilirubin: 0.5 mg/dL

HLA-B5701: negative
How would you modify his ART today?

A. Discontinue raltegravir and change to dolutegravir 50 mg once daily. Continue tenofovir DF 300 mg once weekly, darunavir 800 mg once daily, ritonavir 100 mg once daily

B. Discontinue all current antiretrovirals and start dolutegravir 50 mg once daily and Descovy® (tenofovir AF/emtricitabine 25/200 mg) once daily

C. Discontinue all current antiretrovirals and start dolutegravir 50 mg once daily, lamivudine 50 mg x 1 dose then 25 mg daily after HD, and abacavir 600 once daily

D. Discontinue all current antiretrovirals and start Triumeq® (dolutegravir/abacavir/lamivudine 50/600/300 mg) once daily
What information about your recommended ART should you relay to his inpatient team for peri-transplant management?

A. Dolutegravir inhibits metabolism of tacrolimus, empirically reduce tacrolimus dose to 0.5 mg once weekly and monitor levels.

B. Lamivudine dose should be adjusted as the patient’s renal function improves post-kidney transplant.

C. Abacavir dose should be adjusted as the patient’s renal function improves post-kidney transplant.

D. Can start single-tablet regimen of Triumeq® (dolutegravir/abacavir/lamivudine 50/600/300 mg) once daily on post-op day 1.
Patient Case

Current medications:
Nifedipine XL 90 mg once daily
**Atorvastatin 20 mg daily**
Aspirin 81 mg daily
Cinacalcet 90 mg daily
Sevelamer 800 mg three times daily with meals

- Consider other medications that may need dose adjustments when changing ART
- Consider increasing atorvastatin to 40-80 mg with discontinuation of darunavir/ritonavir
JR has a KTX offer. Current PRA is 80% and CD4+ count is 450 cells/mm³. What is your recommendation for induction?

A. No induction
B. Anti-thymocyte globulin
C. Basiliximab
What maintenance immunosuppression regimen do you recommend?

A. Tacrolimus, prednisone
B. Tacrolimus, mycophenolate mofetil, prednisone
C. Cyclosporine, mycophenolate mofetil, prednisone
D. None of the above
Acknowledgements

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- Christine Durand, MD
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