“The Patient” Does Not Exist:
Individualized Care of the Solid Organ Transplant Recipient

Stacy A. Crow, Pharm.D., BCPS

Pharmacy Grand Rounds
November 22, 2016
Learning Objectives

• Explain differences between sub-therapeutic, therapeutic, and supra-therapeutic drug levels considering patient-specific parameters

• Identify drug-drug interactions between immunosuppressant medications and other medicinal therapies

• Discuss different patient scenarios affecting transplant patients and conceptualize how they may alter immunosuppressive approaches
Declarations and Disclosures

• Declares no financial relationships pertinent to this session

• Declares the following off-label use of medication will be discussed during this presentation:
  • Tacrolimus (immediate- and extended-release)
  • Cyclosporine (modified and non-modified)
  • Mycophenolate mofetil
  • Mycophenolate sodium
  • Azathioprine
  • Prednisone
  • Valganciclovir
  • Anti-thymocyte globulin (equine & rabbit)
  • Basiliximab

• For data from Organ Procurement and Transplantation Network, the following disclosure was requested: This work was supported in part by Health Resources and Services Administration contract 234-2005-37011C. The content is the responsibility of the authors alone and does not necessarily reflect the views or policies of the Department of Health and Human Services, nor does mention of trade names, commercial products, or organizations imply endorsement by the U.S. Government.
Solid Organ Transplantation at a Glance

• 119,922 in the United States are listed
• 27,605 transplants thus far in 2016

Timeline of Immunosuppressants

1954 – Successful renal transplant
• Monozygous transplant – no immunosuppression

1959 – Successful allograft
• Dizygotic twins – total body irradiation

1962 – Successful unrelated allograft
• Azathioprine administered
• Patient lived > 1 year

1963 – Successful treatment of rejection
• High-dose prednisone 200 mg/day

Figure 2. One-year first cadaveric renal allograft survival and rejection episodes

- Radiation
- Prednisone
- 6-MP

- Cyclosporine
  - Tacrolimus
- Mycophenolate
  - Daclizumab
  - Basiliximab
- Thymoglobulin
- Sirolimus
  - Rituximab
  - Alemtuzumab

- Azathioprine
- ATGAM (e-ATG)

- Rejection <12 mo
- 1 Year Survival

Year:
'60 '65 '70 '75 '80 '85 '90 '95 '00 '05

Goal of Immunosuppression

- Target narrow therapeutic index to balance risk of acute rejection with risk of over immunosuppression
  - Changes in the intensity or nature of one component obligates assessment of the other

Diagram:
- Rejection
- Infection
- Too little
- Too much
- Immunosuppression
Balance of Immunosuppression

Rejection versus Toxicity

Tacrolimus Levels and Incidence of Rejection and Creatinine Elevation

Srinivas TR. Transplantation. 1996. 62(7):900-905
Balance of Immunosuppression

Calcineurin Inhibitors Toxic in All Transplant

Figure 1. Cumulative Incidence of Chronic Renal Failure among 69,321 Persons Who Received Nonrenal Organ Transplants in the United States between January 1, 1990, and December 31, 2000.

The risk of chronic renal failure was estimated with a noncompeting-risk model. Measurements of renal function were obtained at six-month intervals during the first year and annually thereafter.

Ojo, et al. NEJM.2003. 349(10)
Balance of Immunosuppression

Relationship of Drug Exposure and Rejection

Phases of Immunosuppression

• Induction
  • Reduce T cells response to alloantigens, thus blunting early immune activation
  • Medications are poly- or monoclonal antibodies
    • Anti-thymocyte globulin, basiliximab, etc.

• Maintenance
  • Sustain immunosuppression by balancing efficacy (lack of rejection) and toxicity (acute or chronic)
  • Medications are pathway inhibitors
    • Calcineurin inhibitors, mammalian target of rapamycin inhibitors, anti-metabolites, steroids
Therapeutic Drug Monitoring
Monitoring of Immunosuppressants

• **Half-life**
  • Period of time required for the concentration or amount of drug in the body to be reduced by one-half

• **Trough (C₀)**
  • Lowest level of drug present in the body

• **C₂**
  • Concentration of drug in the blood 2 hours after the dose

• **Cmax**
  • Maximum concentration after the drug has been administrated and prior to administration of a second dose

• **Tmax**
  • Time at which Cmax is observed

• **Area under the curve (AUC)**
  • Total drug exposure over time
Calcineurin Inhibitors
Cyclosporine and Tacrolimus
# Pharmacokinetics of Cyclosporine

<table>
<thead>
<tr>
<th><strong>Cyclosporine (Non-modified and Modified)</strong></th>
<th></th>
</tr>
</thead>
</table>
| **Bioavailability**                         | Non-modified: poor and erratic 10-89%  
                                      | Modified: average 23% higher, less dependent on food, bile acids, and GI motility |
| **Distribution**                            | 90% protein bound (lipoproteins); P-glycoprotein (Pap)/ ABCB1-gene substrate |
| **Metabolism**                              | Liver – CYP3A4 |
| **Elimination**                             | $T \frac{1}{2} \sim 10$ hours |
| **Goal range (ng/ml)**                      | $C_0$ 100 – 350  
                                      | $C_2$ 800 – 1500 |
| **PO to IV**                                | 3 to 1 conversion |

Drugs. 2003. 63(12):1247-1297  
Transplant International. 1998. 11(1) Supp:S94-S97  
Drugs. 2014 Online ahead of print. 29 Oct 2014
Pharmacokinetics (PK) of Cyclosporine

Cyclosporine (CsA) non-modified versus modified

Stabilization in PK profile due to improved bioavailability

## Pharmacokinetics of Cyclosporine

<table>
<thead>
<tr>
<th>Pharmacokinetics</th>
<th>Non-modified and Modified</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bioavailability</strong></td>
<td>Non-modified: poor and erratic 10-89%</td>
</tr>
<tr>
<td></td>
<td>Modified: average 23% higher, less dependent on food, bile acids, and GI motility</td>
</tr>
<tr>
<td><strong>Distribution</strong></td>
<td>90% protein bound (lipoproteins); P-glycoprotein (Pap)/ ABCB1-gene substrate</td>
</tr>
<tr>
<td><strong>Metabolism</strong></td>
<td>Liver – CYP3A4</td>
</tr>
<tr>
<td><strong>Elimination</strong></td>
<td>$T\frac{1}{2} \sim 10$ hours</td>
</tr>
<tr>
<td><strong>Goal range (ng/ml)</strong></td>
<td>$C_0$ 100 – 350  $C_2$ 800 – 1500</td>
</tr>
<tr>
<td><strong>PO to IV</strong></td>
<td>3 to 1 conversion</td>
</tr>
</tbody>
</table>

*Drugs. 2003. 63(12):1247-1297*

*Transplant International. 1998. 11(1) Supp:S94-S97*

*Drugs. 2014 Online ahead of print. 29 Oct 2014*
Therapeutic Drug Monitoring

*Cyclosporine*

- $\text{AUC}_{0-4h}$
  - Maximal immunosuppressive effect of CsA
  - Most variable period
  - Correlates with rejection and nephrotoxicity
    - Non-therapeutic $\text{AUC}_{0-4h} = 45\%$ rejection
    - Therapeutic $\text{AUC}_{0-4h} = 3\%$ rejection ($p=0.0002$)

- $C_2$
  - Single time best correlated with $\text{AUC}_{0-4h}$ ($r^2 0.81-0.93$)

- $C_0$
  - Trough lacked correlation with $\text{AUC}_{0-4h}$ ($r^2 0.03-0.41$)
  - No correlation with toxicity or acute rejection

# Pharmacokinetics of Tacrolimus

<table>
<thead>
<tr>
<th></th>
<th>Immediate-Release</th>
<th>Extended-Release</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bioavailability</strong></td>
<td>Poor and variable 14-32%</td>
<td>AUC = immediate release, ↓Cmax and ↑Tmax</td>
</tr>
<tr>
<td></td>
<td>Consistently take with or without food</td>
<td>Food ↓AUC and Cmax by ~25%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Take in AM &gt;1 hours before or 2-3 hours after breakfast</td>
</tr>
<tr>
<td><strong>Distribution</strong></td>
<td>99% protein bound; PgP substrate</td>
<td>99% protein bound; PgP substrate</td>
</tr>
<tr>
<td><strong>Metabolism</strong></td>
<td>Liver – CYP3A4 &amp; 3A5</td>
<td>Liver – CYP3A4 &amp; 3A5</td>
</tr>
<tr>
<td><strong>Elimination</strong></td>
<td>T ½ ~ 10 hours</td>
<td>T ½ ~ 35-40 hours</td>
</tr>
<tr>
<td><strong>Goal range (ng/ml)</strong></td>
<td>4 - 15</td>
<td>4 – 15</td>
</tr>
<tr>
<td><strong>PO to IV</strong></td>
<td>4 to 1 conversion</td>
<td>4 to 1 conversion</td>
</tr>
<tr>
<td><strong>PO to SL caps</strong></td>
<td>2 to 1 conversion</td>
<td>Not applicable</td>
</tr>
</tbody>
</table>


Drugs. 2003. 63(12):1247-1297
Drugs. 2014 Online ahead of print. 29 Oct 2014
Antimetabolites
Mycophenolate Mofetil and Azathioprine
# Pharmacokinetics

## Anti-metabolites

<table>
<thead>
<tr>
<th></th>
<th>Mycophenolate mofetil</th>
<th>Azathioprine</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Absorption</strong></td>
<td>Bioavailability &gt; 90%</td>
<td>Bioavailability well absorbed</td>
</tr>
<tr>
<td><strong>Food concerns</strong></td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td><strong>Distribution</strong></td>
<td>Protein binding &gt; 90%</td>
<td>Protein binding ~ 30%</td>
</tr>
<tr>
<td><strong>Metabolism</strong></td>
<td>Hydrolyzed in liver then to inactive metabolite via glucuronidation</td>
<td>Metabolized to 6-mercaptopurine via reduction; further metabolized via 1 of 3 major pathway, 2 producing inactive metabolites and 1 producing an active metabolite</td>
</tr>
<tr>
<td><strong>Elimination</strong></td>
<td>$T_{1/2} \sim 18$ hours</td>
<td>$T_{1/2}$ variable $\sim 2$ hours</td>
</tr>
<tr>
<td><strong>PO to IV</strong></td>
<td>1 to 1 conversion</td>
<td>1 to 1 conversion</td>
</tr>
</tbody>
</table>
Therapeutic Drug Monitoring

*Mycophenolic acid*

MPA exposure is best represented by AUC

Therapeutic Drug Monitoring

*Mycophenolic Acid*

- AUCs of Rejectors
- Lower End of Target AUC: 30 mcg•hr/L
- AUCs of Non-Rejectors

**MPA AUC (mcg•hr/L) with Modified CsA**

Therapeutic Drug Monitoring
Azathioprine – Not Routinely Done

Davila L, Ranganathan P. Nature Reviews Rheumatology. 2011. 7:537-550

Thiopurine Methyltransferase
Therapeutic Drug Monitoring

*mTORs*

<table>
<thead>
<tr>
<th></th>
<th>Sirolimus</th>
<th>Everolimus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absorption</td>
<td>Bioavailability liquid ~ 14%, tablets ~ 27%</td>
<td>Bioavailability ~ 16%</td>
</tr>
<tr>
<td>Food concerns</td>
<td>Take consistently</td>
<td>Take consistently</td>
</tr>
<tr>
<td></td>
<td>Fatty meal = ↑Tmax, ↑AUC</td>
<td>Fatty meal = ↓Tmax, ↓AUC</td>
</tr>
<tr>
<td>Distribution</td>
<td>Protein binding ~ 90%</td>
<td>Protein binding ~ 74%</td>
</tr>
<tr>
<td>Metabolism</td>
<td>CYP3A4, PgP</td>
<td>CYP3A4, Pap</td>
</tr>
<tr>
<td>Elimination</td>
<td>T ½ ~ 60 hours</td>
<td>T ½ ~ 30 hours</td>
</tr>
<tr>
<td>Goal range</td>
<td>6 – 12 ng/ml</td>
<td>3 – 8 ng/ml</td>
</tr>
</tbody>
</table>

Target levels vary based on patient’s organ transplant, tolerance, risk for rejection, infection, malignancy, etc.
Net State of Immunosuppression

- All factors that contribute to risk for rejection and infection
  - Immunosuppressive therapies (current and past)
  - Prior therapies (chemotherapy, antimicrobials)
  - Mucocutaneous barrier integrity (catheters, lines, drains)
  - Neutropenia, leukopenia
  - Underlying immune deficiencies
  - Metabolic co-conditions (malnutrition, diabetes)
  - Viral co-infection (CMV, HCV, etc.)
  - Presence of donor specific antibodies

Fishman JA. AJT. 2009. 9;s4:S3-S4
Patient Presentation #1
Patient CD

- 42-year old Caucasian male 5 years post living related kidney transplant
  - Presents to clinic with 4 days of nausea and diarrhea (7 episodes/day)
  - Serum creatinine 2.6 mg/dl (baseline 1.2), tacrolimus level 12.8 ng/ml, hyperkalemic
  - Recent urinary tract infection treated with levofloxacin for 7 days with last tablet taken yesterday
Assessment Question #1

The net state of immunosuppression is patient specific. Which of the following would be useful to know to assess the appropriateness of this patient’s tacrolimus level?

A. Rejection & infection histories
B. Induction agent(s) used at transplant
C. All concomitant medications and doses
D. A & C only
E. A, B, & C
Effect of Diarrhea on Tacrolimus

- Absorption
  - Shifts from ileum to colon where metabolic capacity is decreased
  - Prolongation of Tmax
- Metabolism
  - Increased transit time
  - Ability to metabolize in the ileum is weaker
- Inflammatory changes
  - Intestinal mucosa prevents metabolism by CYP3A4 and P-glycoprotein

Transit time = ↓Metabolism = Elevated TAC Level

Increase in TAC level ~ 3-to-4 fold

Drug-Drug Interactions
### Drug-Drug Interactions with CNIs
**Inhibitors Affecting CNIs and mTORs**

<table>
<thead>
<tr>
<th>Category</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Azole antifungals</strong></td>
<td>Voriconazole, posaconazole, itraconazole, isavuconazole, clotrimazole, fluconazole</td>
</tr>
<tr>
<td><strong>Protease/polymerase inhibitors</strong></td>
<td>Fosamprenavir, ritonavir, dasabuvir, elbasvir, grazoprevir, ombitasvir, paritaprevir, atazanavir</td>
</tr>
<tr>
<td><strong>Non-dihydropyridine calcium channel blockers</strong></td>
<td>Diltiazem and verapamil</td>
</tr>
<tr>
<td><strong>Macrolide antibiotics</strong></td>
<td>Erythromycin, clarithromycin, NOT azithromycin</td>
</tr>
<tr>
<td><strong>Other</strong></td>
<td>Amiodarone, levofloxacin, metronidazole, Antiretrovirals (nevirapine and efavirenz)</td>
</tr>
<tr>
<td><strong>Dietary interactions</strong></td>
<td>Grapefruit juice, pomegranate juice, Sodas: Fresca®, IZZE®, Hansen’s®</td>
</tr>
</tbody>
</table>
## Drug-Drug Interactions

### Inhibitors: Azole Anti-fungals and CNIs

<table>
<thead>
<tr>
<th>Agent</th>
<th>CYP3A4 Inhibitor</th>
<th>Pap Inh.</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluconazole</td>
<td>+</td>
<td>-</td>
<td>CYP inhibition at doses &gt; 150 mg Renal Elimination</td>
</tr>
<tr>
<td>Clotrimazole</td>
<td>++</td>
<td>+</td>
<td>Trough concentrations of TAC + clotrimazole ~ 3-fold higher than tacrolimus + nystatin (p&lt;0.05)</td>
</tr>
<tr>
<td>Isavuconazole</td>
<td>+++</td>
<td>+</td>
<td>Case reports suggesting decrease CNI up to ~50%</td>
</tr>
<tr>
<td>Itraconazole</td>
<td>+++</td>
<td>+</td>
<td>Dose-dependent inhibition of CYP3A4 by metabolites and parent compound, decrease CNI by ~50%</td>
</tr>
<tr>
<td>Voriconazole</td>
<td>+++</td>
<td>+/-</td>
<td>Concentration-dependent inhibition due to intestinal isoenzymes, decrease CNI by ~50-66%</td>
</tr>
<tr>
<td>Posaconazole</td>
<td>++++</td>
<td>+</td>
<td>Recommend decreasing CNI dose by 66%</td>
</tr>
<tr>
<td>Ketoconazole</td>
<td>++++</td>
<td>+</td>
<td>Small doses cause significant CYP3A4 inhibition, additional interaction is also dose-dependent</td>
</tr>
</tbody>
</table>

Choy M. P T. 2010. 35(10): 568-569
### Drug-Drug Interactions

#### Inducers: Additional Agents and CNIs

<table>
<thead>
<tr>
<th>Category</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anticonvulsants</strong></td>
<td>- Phenytoin, phenobarbital, primidone, carbamazepine</td>
</tr>
<tr>
<td><strong>Antimicrobials</strong></td>
<td>- Nafcillin, rifampin, rifabutin, rifapentine</td>
</tr>
<tr>
<td><strong>Miscellaneous</strong></td>
<td>- Methadone</td>
</tr>
<tr>
<td></td>
<td>- St. John’s Wort</td>
</tr>
<tr>
<td></td>
<td>- Antiretrovirals – nevirapine, efavirenz</td>
</tr>
</tbody>
</table>
Solid Organ Transplant Patient Pearls

*Patient Presentations*
Patient Presentation #2
*Tacrolimus Toxicity*

**Subjective:**
- 36-year-old female post pancreas-kidney transplant, recently unwell, reports starting on antibiotic, tremulous

**Objective:**
- Elevated serum creatinine, hyperkalemic, tacrolimus levels climbing upward

**Assessment:**
- Tacrolimus level elevated (>20)

**Plan for Immunosuppression:**
- To be determined
Patient Presentation #2
Tacrolimus Toxicity: Assessment of Immunosuppression

• Current value:
  • Type of level being analyzed
    • Trough, C2, a different time point
  • When was the last dose?
  • Is the timing of the draw appropriate?
  • Missed or extra doses?
  • Changes in dietary intake
  • New interactions (or lack thereof) or explanations

• If grossly elevated, consider holding ≥1 dose of immunosuppressant, discontinue interacting agent if able, potential administration of inducer
Patient Presentation #2
Tacrolimus Toxicity: Therapeutic Enzymatic Induction

• Patients
  • Four transplant patients with symptomatic TAC toxicity (troughs >30 ng/ml) with gastro-intestinal symptoms, hyperkalemia, and acute renal failure

• Intervention
  • Phenytoin 300-400 mg/day x 2-3 days

• Result
  • Rapid decrease in tacrolimus level to < 15 ng/ml
  • Rapid reversal of renal dysfunction with measurements of serum creatinine at or near baseline
  • No phenytoin side effects

Jantz AS et al. Case reports in Transplantation. 2013
Patient Specific Scenarios

Tacrolimus Toxicity: Therapeutic Enzymatic Induction

Jantz AS et al. Case reports in Transplantation. 2013
Assessment Question #2

76-year-old female liver/kidney transplant patient 12 years post transplant presents via the ED with complaints of dysuria and tenderness over her kidney graft. SCr slightly elevated to 1.6 (baseline 1.2-1.4). Medications include:

- Cyclosporine (CsA) 75mg po q12h
- MMF 1g po daily
- Nifedipine XL 60mg daily
- Pantoprazole 40 mg daily
- Prednisone 2.5mg po daily

CsA level at clinic 3 days ago ~100 ng/ml

Morning labs come back and report a CsA level of 185 ng/ml. The reported lab draw time is 0745, and the nurse is not sure if the morning dose was given prior to the level.
Assessment Question #2

The reported CsA level may or may not have been drawn after the morning dose. Which of the following is the best course of action?

A. Order a STAT cyclosporine level to reassess

B. Decrease to CsA 50mg po q12h; the patient has diarrhea, which can increase CsA

C. Hold the evening CsA dose; obtain a cyclosporine level the next morning, prior to the dose

D. Continue CsA 75mg po q12; obtain a level the next morning, prior to the dose
Patient Presentation #3
Genetic Considerations

57-year-old African-American male post heart transplant 9/30/2014 with a non-contributory past medical history admitted to your inpatient service on the weekend

• Medication history reports immunosuppressants as:
  - Mycophenolate mofetil 1.5g twice daily
  - Prednisone 10mg daily
  - Tacrolimus 12mg three times daily
  - *Noteworthy drug interaction: ketoconazole 200mg twice daily*
Genetic Considerations

Patient CW

TAC level (ng/ml)

Total daily TAC dose

Genetic alteration: CYP3A5*1/*1
Genetic Considerations

Cytochrome P-450

- Predominantly CYP3A4 and CYP3A5
- Alterations most common in patients of African, Asian, Middle Eastern and Hispanic decent

- Cheung CY, et al.
  - CYP3A5*1 expressers (homozygous or heterozygous) require ~ 2x higher tacrolimus dose to maintain goal range compared with non-expressers
  - Pre-emptive genetic testing strategies available
  - **Clinical significance?**

Assessment Question #3

Patient GT is a 30-year-old male who presents to the service that you are covering.

Past medical history indicates a CYP3A5*1. The rounding physician is unfamiliar with pharmacogenomics and want to know how this may impact tacrolimus dosing.
Assessment Question #3

Some genetic alterations may affect metabolism of tacrolimus (TAC). Which of the following would be correct to tell the physician about GT’s tacrolimus dosing requirements relative to patients with standard genomics?

A. May require smaller doses of TAC and an inhibitor like rifampin
B. May require smaller doses of TAC and an inhibitor like ketoconazole
C. May require larger doses of TAC and an inhibitor like rifampin
D. May require larger doses of TAC and an inhibitor like ketoconazole
Conclusions and Caveats

• No two transplant patients are created equal, essential to treat the individual

• Immunosuppression requires constantly balancing the risks and benefits of over- and under-immunosuppression

• Successful immunosuppression utilizes a multi-modal approach to therapy, an appropriate assessment considers all factors affecting the net immunosuppression

• Convenience for the individual is essential!
Questions & Discussion

THANK YOU for the Gift of Life!
Register to be a donor!
### Additional Azole Drug-Interaction

Table 2. Recommended Percentage Dose Reductions of Immunosuppressants During Concomitant Azole Therapy\(^{24, 25, 40, 69-71}\)

<table>
<thead>
<tr>
<th>Azole</th>
<th>Cyclosporine</th>
<th>Tacrolimus</th>
<th>Sirolimus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ketoconazole</td>
<td>70–80</td>
<td>50–60</td>
<td>80–90</td>
</tr>
<tr>
<td>Fluconazole</td>
<td>21–50(^{a})</td>
<td>40(^{b})</td>
<td>50–70(^{c})</td>
</tr>
<tr>
<td>(≥ 200 mg/day)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Itraconazole</td>
<td>50–60</td>
<td>50–60</td>
<td>No data</td>
</tr>
<tr>
<td>Voriconazole</td>
<td>50</td>
<td>66(^{d})</td>
<td>90(^{e})</td>
</tr>
<tr>
<td>Posaconazole</td>
<td>0–30(^{f})</td>
<td>75–80(^{f, g})</td>
<td>No data(^{g})</td>
</tr>
</tbody>
</table>

\(^{a}\)Extent of interaction depends on the route of administration of cyclosporine (see text).

\(^{b}\)Based on studies of low-dose fluconazole 100 mg/day.

\(^{c}\)Based on limited data (see text).

\(^{d}\)Variable (see text).

\(^{e}\)Used in clinical practice. Coadministration is contraindicated according to the manufacturer (see text).

\(^{f}\)Based on limited data (see text).

\(^{g}\)At the time of writing.

Saad AH, et al. Pharmacotherapy. 2006. 26(12);1730-1744
Drug-Drug Interactions
**CNIs and Statin**

- With CsA - Increased systemic exposure of atorvastatin and metabolites and decreased intestinal PGP and increased intestinal CYP3A4
- With TAC - No impact on atorvastatin pharmacokinetics

### Interaction Potential with CsA

- **Highest**
  - Simvastatin
  - Lovastatin
  - Atorvastatin
  - Rosuvastatin
  - Pitastatin

- **Lowest**
  - Pravastatin

---

Genetic Considerations

PgP

- Located in GI tract

“Neither the individual PgP polymorphisms nor the PgP haplotypes were associated with any pharmacokinetic parameter.”