



Penn Medicine

# Immunosuppression and Medication Adherence after Solid Organ Transplantation

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# Objectives

- ▶ Review common immunosuppressant agents utilized in the care of kidney transplant recipients
- ▶ Highlight interventions that should be promoted by the healthcare team to encourage patient medication adherence

# Immunosuppressive Medications

Medication Class	Medications
Polyclonal Antibodies	Equine Anti-thymocyte globulin (Atgam®) Rabbit Anti-thymocyte globulin (Thymoglobulin®)
Monoclonal Antibodies	Basiliximab (Simulect®)
Calcineurin Inhibitors	Tacrolimus (Prograf®) and generics Tacrolimus extended release capsules (Astagraf XL®) Tacrolimus extended release tablets (Envarsus XR®) Cyclosporine (Sandimmune®) and generics Cyclosporine modified (Neoral®, Gengraf®) and generics
Anti-proliferative Agents	Azathioprine (Imuran®) and generics Mycophenolate mofetil (Cellcept®) and generics Mycophenolic acid – delayed release (Myfortic®) and generics Sirolimus (Rapamune®) and generics Everolimus (Zortress®)
Steroids	Methylprednisolone (Solu-Medrol®) and generics Prednisone (Deltasone®) and generics
Selective T-cell Co-Stimulation blockade	Belatacept (Nulojix®)
Miscellaneous	Alemtuzumab, Rituximab, Bortezomib, Cyclophosphamide, Methotrexate, Immune Globulin, Eculizimab

# Induction Immunosuppression



# Rabbit Anti-Thymocyte Globulin (Thymoglobulin®)

- ▶ Usually 3 to 5 doses
- ▶ Can also be used for treatment of rejection
- ▶ Administered over 6 hours (1<sup>st</sup> dose) or 4 hours (subsequent doses) via central or peripheral line
  - Note: peripheral line infusion contains 1000 units of heparin and 20 mg of hydrocortisone
- ▶ Preventing infusion reactions
  - Release of cytokines by activated monocytes and lymphocytes may lead to cytokine release syndrome during infusion → serious cardiopulmonary events
  - Pre-medications 1 hour prior to dose:
    - Acetaminophen 650 mg orally or rectally
    - Diphenhydramine 50 mg orally or IV
    - Steroids (organ and patient-specific)

# Basiliximab (Simulect®)

- ▶ Two doses of 20 mg IV
  - First dose given in the OR during transplant
  - Second dose given on post-operative day 3 or 4
- ▶ Administered over 30 minutes via central or peripheral line
- ▶ No pre-medications required

# Maintenance Immunosuppression



# Safe Handling of Transplant Medications

- ▶ Transplant medications are life-saving to patients who need them, but may be harmful to people who do not
- ▶ Certain transplant medications are classified as “hazardous”
  - “Hazardous” medications may increase risk of cancer and birth defects
  - Risk of exposure is highest to health care workers and lower for caregivers
- ▶ Regulations require that health care workers wear protection like gloves, masks, or gowns when handling these medications and bodily fluids



# Calcineurin Inhibitors (CNI)

Availability	Tacrolimus	Cyclosporine
Oral Capsules	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>
Oral Liquid	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>
Intravenous	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>
Sublingual administration	<input checked="" type="checkbox"/> ( <i>IR Tac only</i> )	<input checked="" type="checkbox"/>
Generic	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>

## ► Dosing and monitoring

- Usually administered every 12 hours
- Dose adjusted based on trough levels
- Goal trough levels vary by transplanted organ and time post-transplant

# Tacrolimus Sublingual Administration

Open the IR capsules and place the contents of the capsule(s) under the tongue, allowing contents to completely dissolve



Patient should avoid swallowing for 5 to 15 minutes and avoid oral intake for 15 to 30 minutes



Avoid mechanical suctioning for at least 30 minutes after administration

- Not 1:1 conversion from oral to sublingual!
- Only utilize **immediate release (IR)** formulation
- When handling open capsules, wear **powder-free nitrile gloves**

# Once Daily Tacrolimus

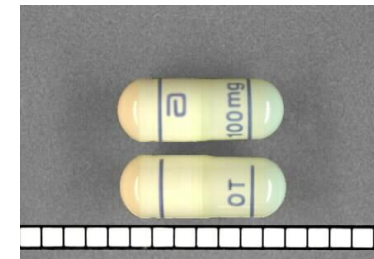
Astagraf XL®	Envarsus XR®
Dose 1:1 conversion of <u>total daily dose of IR</u>	Dose IR → XR = 70-80% total daily IR dose ( <u>Not</u> an equivalent dose conversion of IR)
Taken once daily in the morning	
Take tablets/capsules whole – DO NOT OPEN, CRUSH OR CHEW	



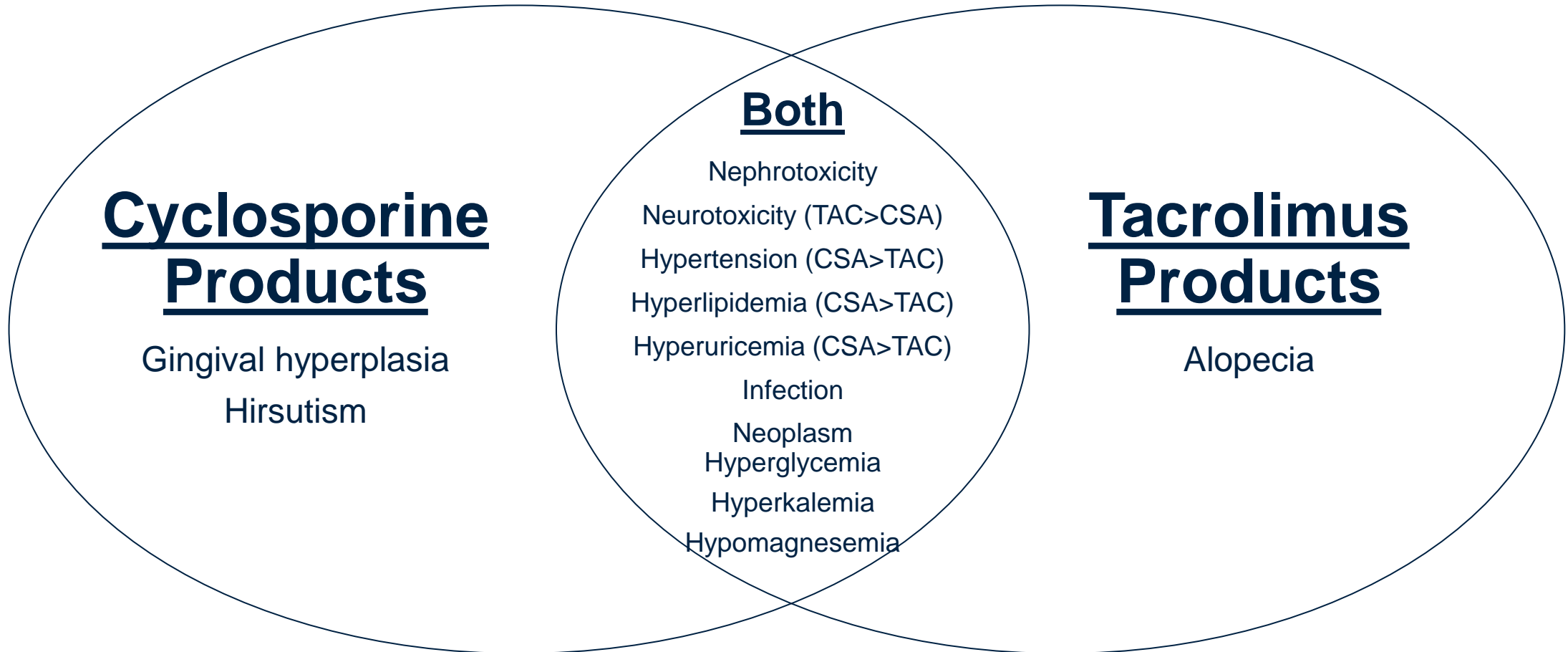
# Cyclosporine

Cyclosporine	Modified	Non-modified
Brand names	Neoral®, Gengraf ®	Sandimmune®
Formulation	<ul style="list-style-type: none"> <li>• Microemulsion formulation</li> <li>• Does not depend upon bile salts for absorption</li> <li>• ↑ bioavailability, more consistent absorption</li> </ul>	<ul style="list-style-type: none"> <li>• Depends upon bile for absorption</li> <li>• Erratic absorption</li> </ul>
Dosage forms	Capsules, solution	Capsules, oral solution, concentrate for injection

NOT bioequivalent



# CNI-Related Side Effects



# Mycophenolate

## Mycophenolate mofetil (MMF/Cellcept®)

### ▶ Preparations

- Intravenous injection
  - IV dose = PO dose
- Oral capsule
- Oral tablet
- Oral liquid
- Generic



## Mycophenolic acid – delayed release (Myfortic®)

### ▶ Preparations

- Oral tablets only
- Generic
- 180 mg Myfortic® = 250 mg MMF

**Dosing: Twice daily**

**Not Interchangeable**



180 mg



360 mg

# Mycophenolate REMS

The FDA determined that a **REMS** (Risk Evaluation and Mitigation Strategy) is necessary to ensure that the benefits of mycophenolate outweigh the risks of first trimester pregnancy loss and congenital malformations associated with mycophenolate use during pregnancy.

## Specifically:

1. Higher risk of miscarriage in the first 3 months
2. Higher risk that the baby will have birth defects



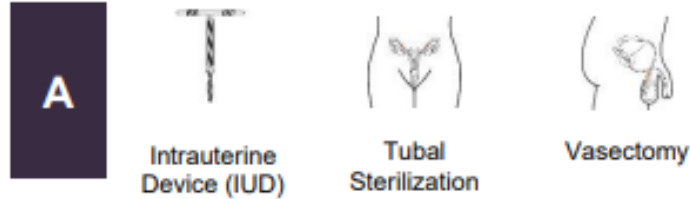
# Mycophenolate REMS

## ACCEPTABLE BIRTH CONTROL OPTIONS

Talk with your doctor and pick from the following birth control options during treatment with mycophenolate.

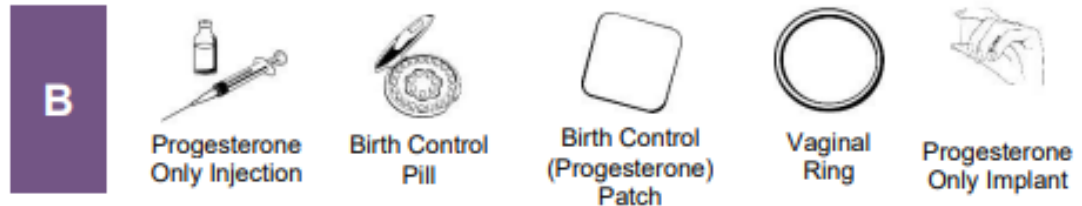
### Option 1 | Use Method Alone

- Pick one item from (A)
  - ▶ **Most effective:** Less than 1 pregnancy per 100 women in one year



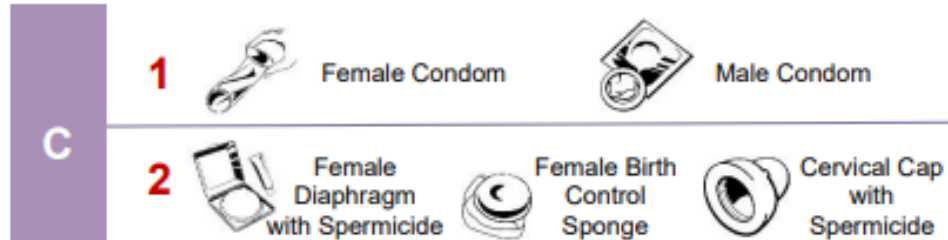
### Option 2 | Use Hormone & Barrier

- Pick one item from (B) **and** one item from (C1) or (C2) shown below
  - ▶ 4-7 pregnancies per 100 women in one year



### Option 3 | Use Two Barriers

- Pick one item from (C1) **and** one from (C2)
  - ▶ **Least effective:** 13 or more pregnancies per 100 women in one year



To learn more about all the risks of taking mycophenolate, please see the Medication guide, which can be found at [MycophenolateREMS.com](http://MycophenolateREMS.com)



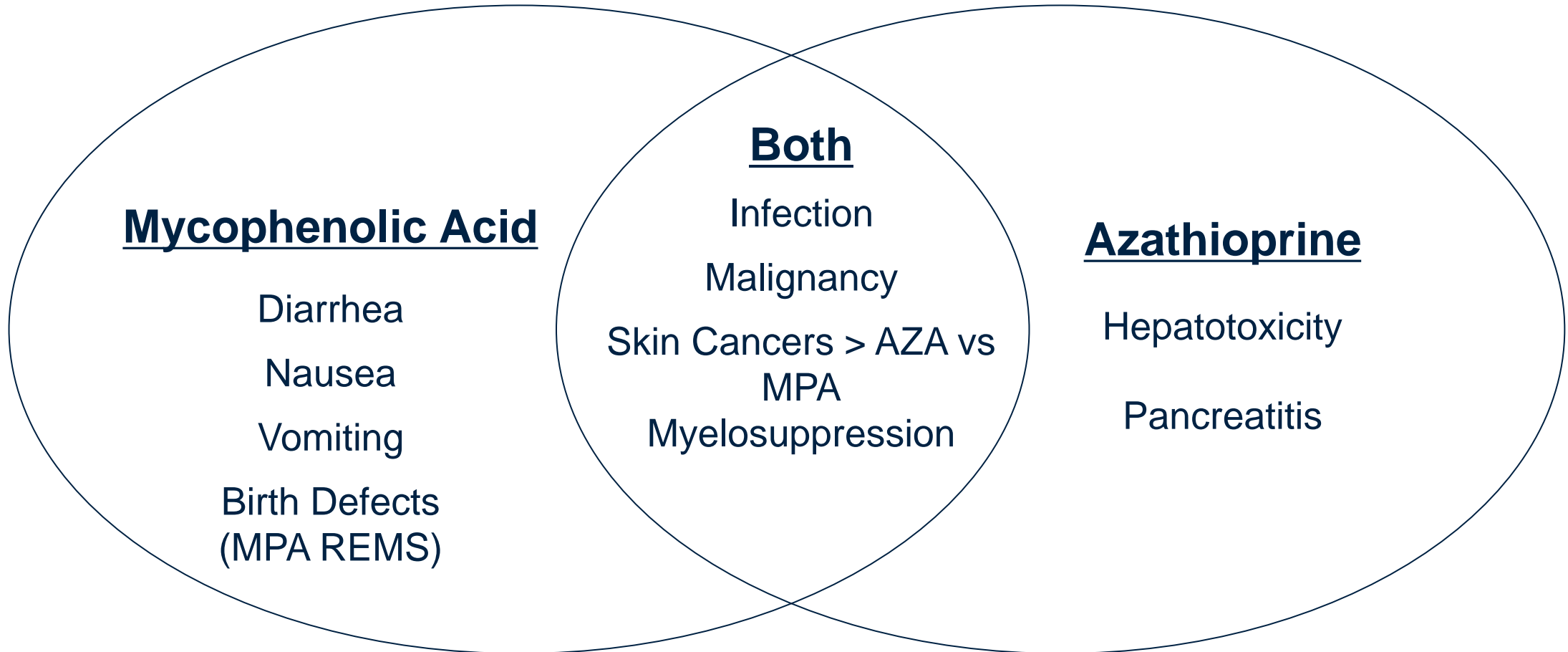


# Azathioprine (Imuran<sup>®</sup>)

- ▶ Administered once **daily**
- ▶ **Do NOT crush**
- ▶ Formulation
  - Oral tablets (Imuran<sup>®</sup> and Azasan<sup>®</sup> = \$\$\$)
  - Generic tablets
  - Oral suspension (pharmacy)
  - Intravenous injection
- ▶ Drug interactions
  - Allopurinol
  - Febuxostat



# Anti-Proliferative: Adverse Events



# Corticosteroids

- ▶ Given intravenously (methylprednisolone) and then transitioned to oral therapy (prednisone)
  - May eventually be discontinued in some organs
  - Methylprednisolone:prednisone conversion is 4:5
- ▶ Can also be used for treatment of rejection
- ▶ Dosing and taper schedule depends on organ transplanted and patient factors

# Steroid Side Effects

System	Effects
Neurologic	Euphoria, depression, psychosis, emotional lability
Cardiovascular	Hypertension
Endocrine	Hyperglycemia, increased appetite, osteoporosis
Musculoskeletal & skin	Thinning of skin, poor wound healing, thin arms/legs due to muscle wasting, increased abdominal and upper back fat

# Steroid Side Effects – Acute/Higher dose

System	Effects
Neurologic	<b>Euphoria, depression, psychosis, emotional lability</b>
Cardiovascular	<b>Hypertension</b>
Endocrine	Hyperglycemia, <b>increased appetite</b> , osteoporosis
<b>Musculoskeletal &amp; skin</b>	Thinning of skin, poor wound healing, thin arms/legs due to muscle wasting, increased abdominal and upper back fat

# Steroid Side Effects – Chronic Use

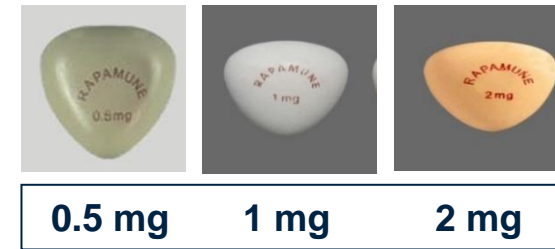
System	Effects
Neurologic	Euphoria, depression, psychosis, emotional lability
Cardiovascular	Hypertension
Endocrine	<b>Hyperglycemia</b> , increased appetite, <b>osteoporosis</b>
Musculoskeletal & skin	<b>Thinning of skin, poor wound healing, thin arms/legs due to muscle wasting, increased abdominal and upper back fat</b>

# Sirolimus and Everolimus

▶ Can replace or reduce CNI or antimetabolite (mycophenolate or azathioprine)

▶ Sirolimus (Rapamune®) and generics

- Usually administered once daily
- Available in tablets and oral solution



▶ Everolimus (Zortress®)

- Usually administered two times daily
- Available only as tablets



# Sirolimus and Everolimus

## ▶ DO NOT CRUSH

## ▶ Monitored by trough levels

## ▶ Side effects

- Delayed wound healing → must HOLD  $\geq 7$  days prior to surgery
- Hyperlipidemia
- Proteinuria
- Peripheral edema
- Interstitial lung disease
- Mouth ulcerations



# Belatacept (Nulojix<sup>®</sup>)

- ▶ Approved for use in kidney transplant recipients
- ▶ Weight-based dosing
  - 10 mg/kg doses 1 through 6, then 5 mg/kg (maintenance)
- ▶ Administered by IV infusion over 30 minutes
- ▶ Dosing Schedule
  - Days 1 and 5
  - Weeks 2, 4, 8, and 12 post-transplant
  - Maintenance doses given every 4 weeks
- ▶ Assess for altered mental status or memory losses with each dose

# Individualizing Immunosuppression Regimens

- ▶ Efficacy
  - Short-term
  - Long-term
- ▶ Toxicity
  - Short-term
  - Long-term
- ▶ Risk Factors
- ▶ Adherence
- ▶ Cost



# Other Common Medications

- Opportunistic infection prophylaxis
- Pain after surgery
- Constipation
- Heartburn
- Hyperlipidemia
- Hypertension
- Hyperglycemia or diabetes

# Medication Adherence



# The Plague of Medication Non-Adherence

**“Drugs don’t work if people don’t take them.”**

- C. Everett Koop, 1985

- **Transplantation can no longer accept the status quo**
  - Despite millions in investment, a “magic” drug or procedure to render adherence irrelevant is not on the horizon

# Medication Compliance vs Adherence

## ▶ Compliance

- Passive act of the patient to follow the providers orders

## ▶ Medication Adherence

- Process by which patients take their medications as prescribed, composed of initiation, implementation, and discontinuation
- No consensus on a cutoff to define medication non-adherence (NA)

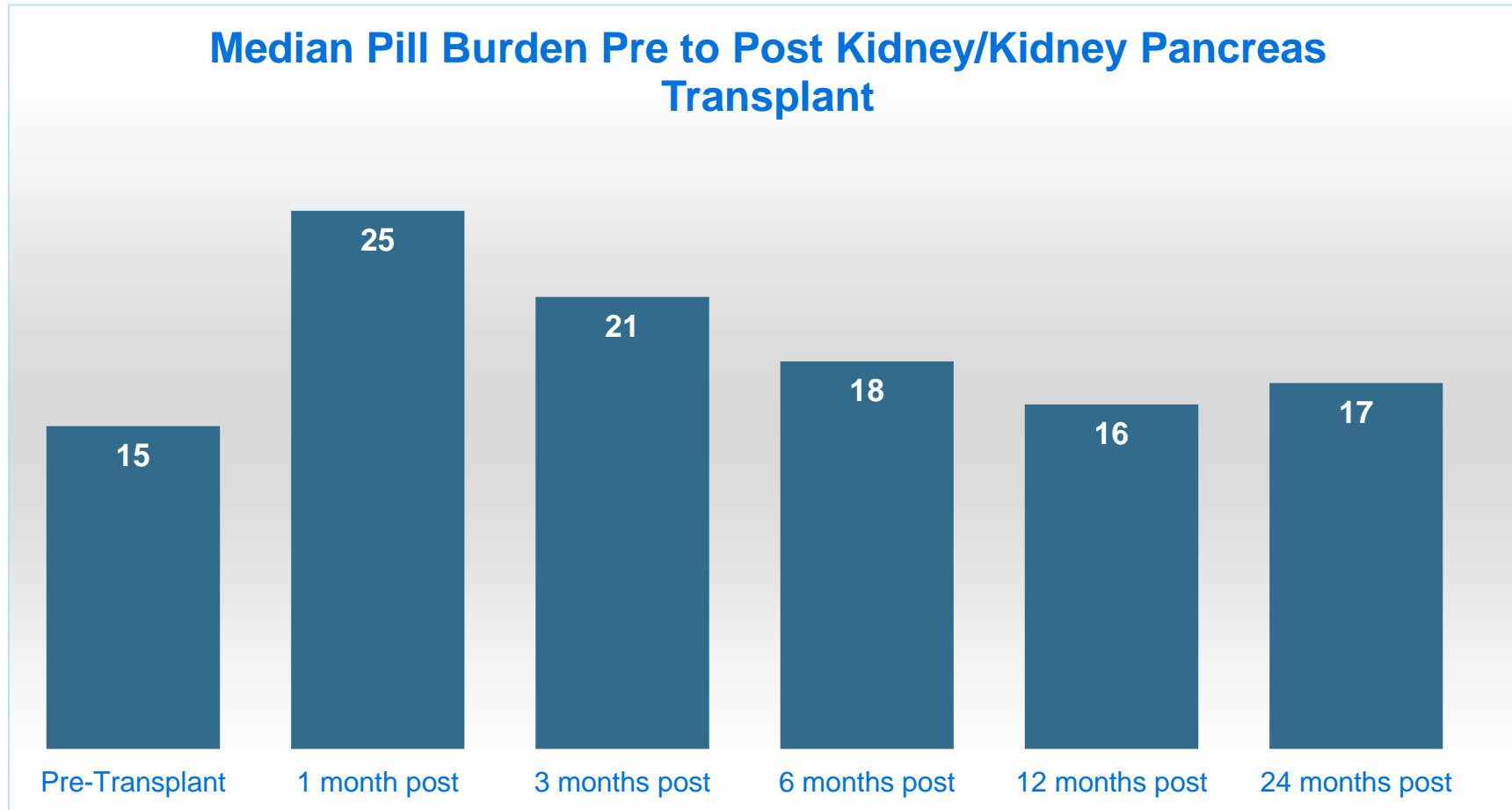
## Question

**What is your estimate of the typical number of medications a transplant recipient is sent home on from transplant admission?**

- A) 6 or less
- B) 7-10
- C) 11-14
- D) 15 or more

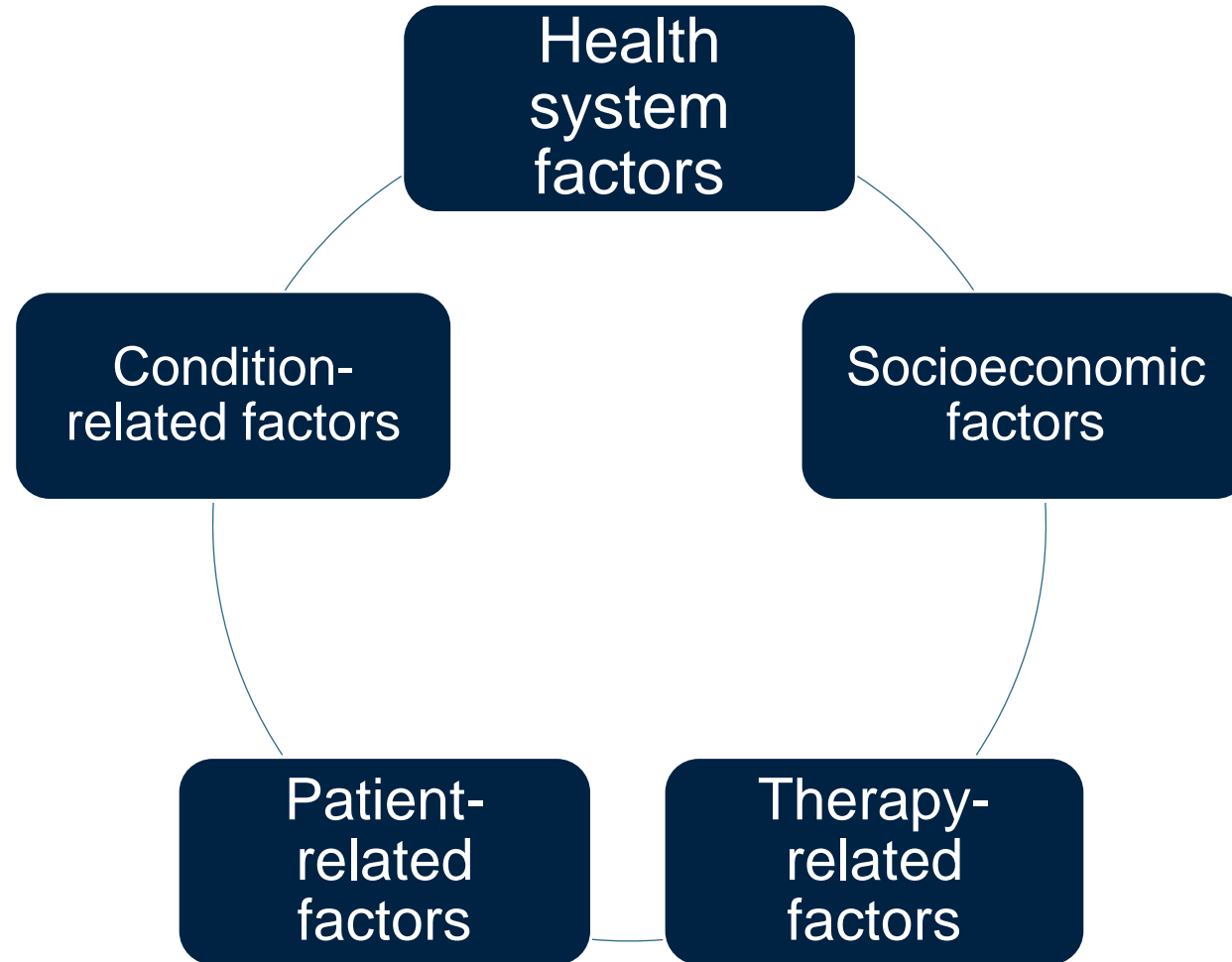


# How Many Pills Will I Take?

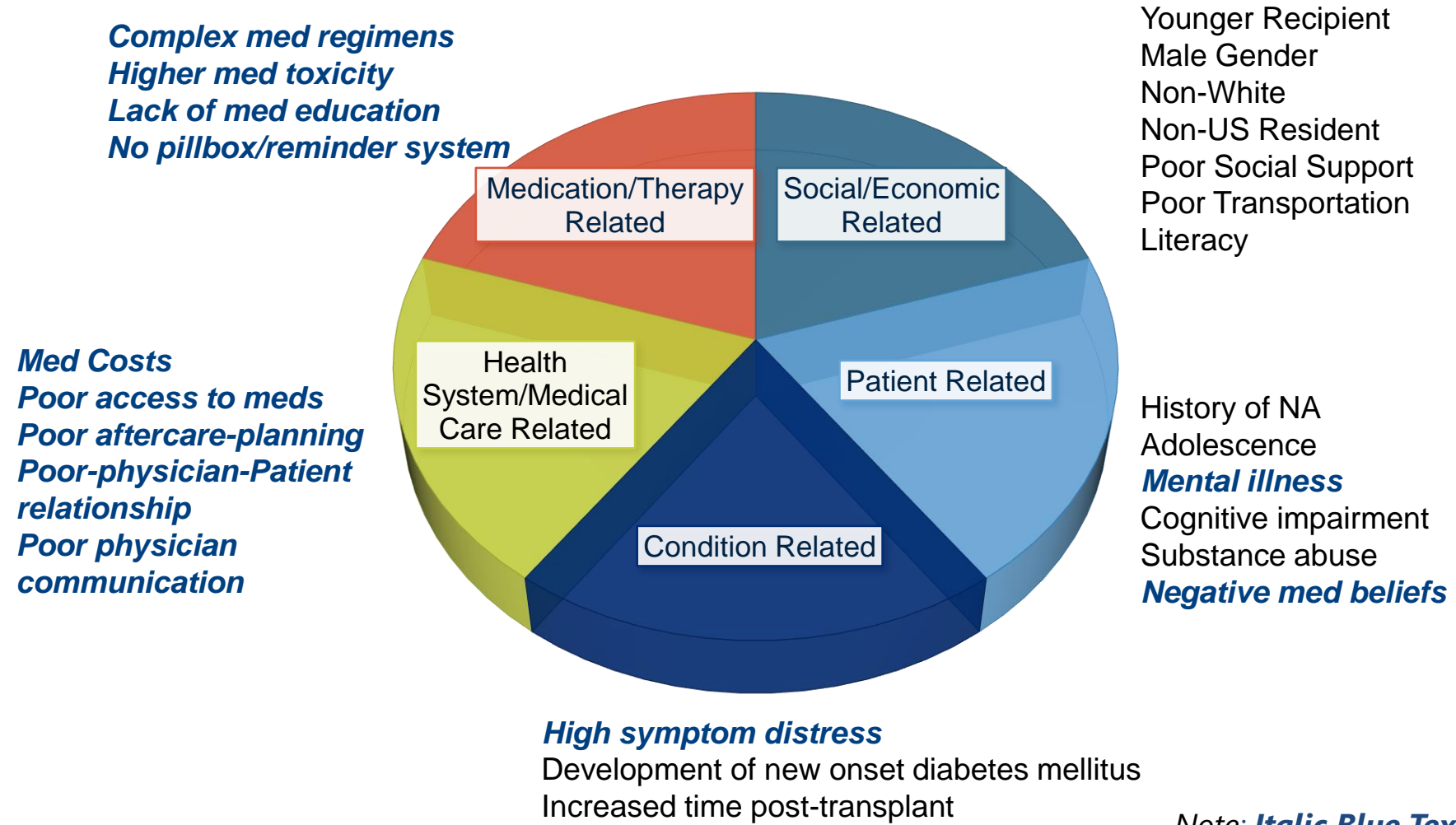




# Reasons for Nonadherence



# Transplant-Specific Factors for Medication Nonadherence



Note: *Italic Blue Text* are Modifiable Factors

# Types of Interventions

Intervention Type*	Notes
<b>Educational</b>	<ul style="list-style-type: none"><li>• Multi-disciplinary (mode and content based on patient factors and time before/after transplant)</li></ul>
<b>Behavioral</b>	<ul style="list-style-type: none"><li>• Contracts</li><li>• Peer mentor and/or support groups</li><li>• Reminder systems (pill boxes, alarms)</li><li>• Rewarding desired behavior</li></ul>
<b>Organizational</b>	<ul style="list-style-type: none"><li>• Simplify regimen complexity</li></ul>
<b>Cognitive Behavioral</b>	<ul style="list-style-type: none"><li>• Motivational interviewing</li><li>• Problem solving skills</li></ul>
<b>Technology-Based</b>	<ul style="list-style-type: none"><li>• Medication list/reminder/tracking apps/texts</li><li>• Wireless electronic medication bottles</li><li>• Biofeedback sensors</li><li>• Telehealth</li></ul>

\* Interventions often combined for a multifaceted approach

# Interventions to Mitigate Medication Nonadherence

## ▶ Medication reconciliation in electronic medical record







- Can the list be simplified?
- Are there duplicate therapies that can be eliminated?

## ▶ Periodically check patient source of medication list

- Provide updated paper version if needed
- Encourage use of apps/electronic resources that auto-update list



# Example MedActionPlan™

Take this medicine	9:00 am	3:00 pm	9:00 pm	Purpose/Notes
 <b>Tacrolimus</b> (Prograf) 1 mg Oral Capsule Take by mouth	<b>3</b> capsules		<b>3</b> capsules	Prevents rejection On day of labs DO NOT take this medicine until after blood draw. Bring dose with you. Your doctor may change your dose during treatment.
 <b>Azathioprine</b> (Imuran) 50 mg Oral Tablet Take by mouth	<b>2</b> tablets			Prevents rejection Take with food to reduce nausea or stomach upset.
 <b>Prednisone</b> 5 mg Oral Tablet Take by mouth	<b>3</b> tablets			Prevents rejection Take with food.
 <b>Acyclovir</b> (Zovirax) 800 mg Oral Tablet Take by mouth	<b>1</b> tablet	<b>1</b> tablet	<b>1</b> tablet	Prevents viral infections
 <b>Sulfamethoxazole/ trimethoprim</b> (Bactrim) 400 mg/80 mg Oral Tablet Take by mouth	<b>1</b> tablet			Prevents bacterial infections Avoid prolonged exposure to the sun.
 <b>Famotidine</b> (Pepcid) 20 mg Oral Tablet Take by mouth	<b>1</b> tablet		<b>1</b> tablet	Prevents and treats heartburn. Prevents and treats stomach ulcers.

# Interventions to Mitigate Nonadherence

- ▶ Medication bottle review and pill box use and review
- ▶ Evaluate medication adherence regularly
  - Identify barriers, confirm use of interventions by patient/caregivers
  - If not using tools, reassess reasons in a non-judgmental manner
- ▶ Assess medication knowledge
- ▶ Provide further tailored-education
  - Consider health literacy level and cognition
  - Use teach back method
  - Involve caregivers as applicable



# Transplant Patient Perspective to Mitigate Nonadherence







- ▶ Tailor interventions to individual vs 1-size-fits-all approach
- ▶ Simplify immunosuppressive regimen
- ▶ Incorporate patient support groups, social media, and 1:1 mentoring of new recipients by experienced ones
- ▶ Address cost and access to medications
- ▶ Incorporate proven interventions into routine care
- ▶ Address negative “sick” stigma with long term immunosuppression that leads to burn-out and depression



# Patient Adherence Tools

- ▶ Medication list (MedActionPlan™)
- ▶ Penn Chart Medication List
- ▶ Pill boxes
  - Remind patient to carry medication with them when not at home

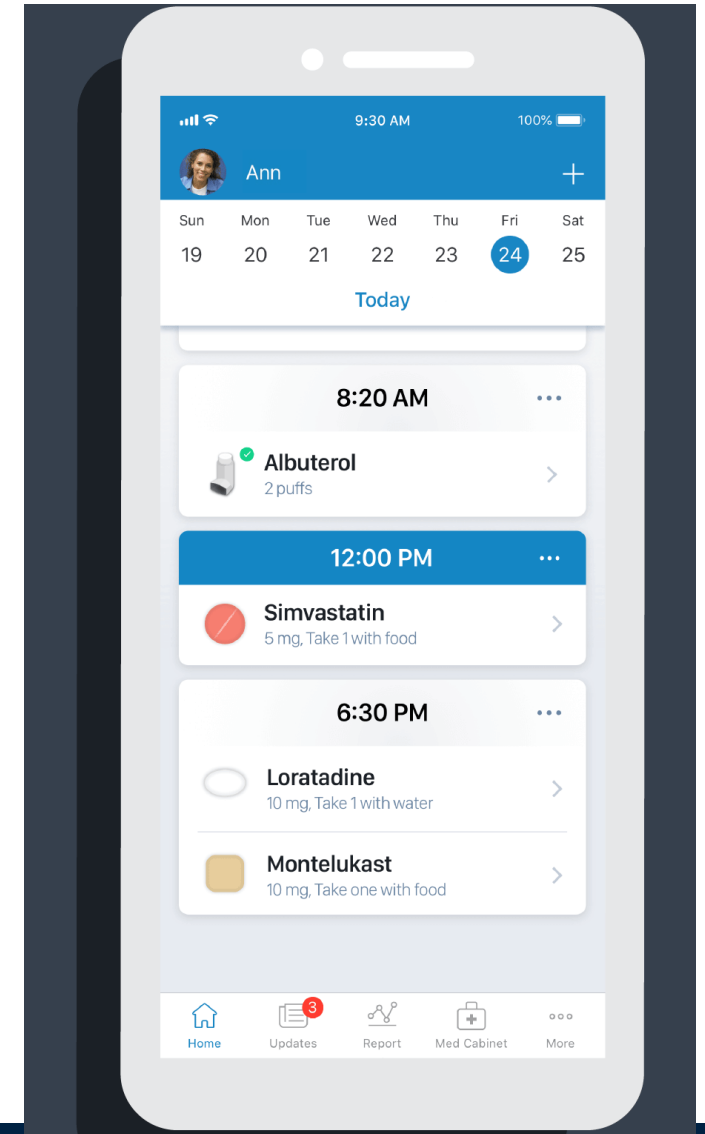
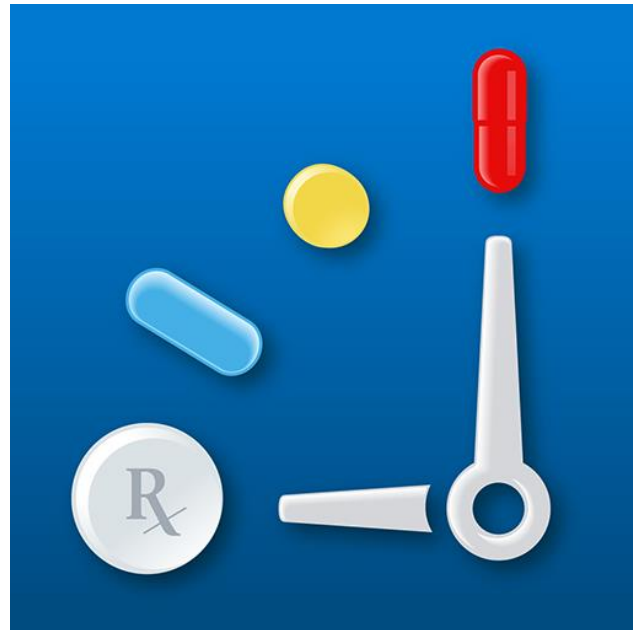


Take this medicine	9:00 am	9:00 pm	Purpose/Notes
 <b>Tacrolimus®</b> (Prograf) 1 mg Oral Capsule Take by mouth	7 capsules	7 capsules	Prevents rejection. <b>**TRANSPLANT MEDICATION**</b> . Take consistently with or without food. Do not drink or eat any product containing grapefruit or pomegranate, starfruit, tangelo, pomelo. On day of labs DO NOT take this medicine until after blood draw. Bring meds with you.
 <b>Mycophenolate mofetil®</b> (Cellcept) 250 mg Oral Capsule Take by mouth	2 capsules	2 capsules	Prevents rejection. <b>**TRANSPLANT MEDICATION**</b> . Do not break, crush, or chew. Avoid prolonged exposure to the sun.
 <b>Prednisone</b> 5 mg Oral Tablet Take by mouth	1 tablet		Prevents rejection. <b>**TRANSPLANT MEDICATION**</b> . Take with food. Do not suddenly stop taking without talking with your doctor.
 <b>Sulfamethoxazole/trimethoprim®</b> (Bactrim) 400 mg/80 mg Oral Tablet Take by mouth	1 tablet		Prevents pneumonia after transplant. Prevents and treats bacterial infections. <b>**ANTIBIOTICS**</b> . Avoid prolonged exposure to the sun. . Take with food to reduce nausea or stomach upset.
 <b>Valganciclovir®</b> (Valcyte) 450 mg Oral Tablet Take by mouth	Take 1 tablet by mouth every other day at 9:00 am.		Prevents cytomegalovirus (CMV) infections. <b>**ANTIBIOTICS**</b> . Do not break, crush, or chew. Take with food.
 <b>Nystatin</b> 100,000 units/mL Oral Suspension Swish and swallow	Swish and swallow 5 mL (1 teaspoon) 3 times every day after meals.		Prevents and treats fungal infections. <b>**ANTIBIOTICS**</b> . Swish and swallow 30 minutes after meals. Do not eat or drink, including water, for 30 minutes after taking. Shake well.

# Patient Adherence Tools

## ► Medication reminders

- Phone alarms
- Phone apps
  - Medisafe
  - My Med Schedule Mobile



# Patient Adherence Tools

- ▶ Counseling at all points of contact
- ▶ Education with each drug administration
- ▶ Reinforcement!

Questions?



