Public Meeting on Patient-Focused Drug Development for Patients Who Have Received an Organ Transplant

September 27, 2016

U.S. FOOD & DRUG ADMINISTRATION

Welcome

Meghana Chalasani
Office of Strategic Programs
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

September 27, 2016

Agenda

- Setting the context
  - Overview of FDA's Patient-Focused Drug Development
  - Overview of Organ Transplant and Available Post-Transplant Treatment Options
  - Road from PFDD Meetings to Clinical Trial Endpoints
  - Overview of Discussion Format
- Topic 1 Discussion
- Topic 2 Discussion
- Lunch
- Scientific Discussion
- Open Public Comment
- Closing Remarks

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Opening Remarks

Edward Cox, MD, MPH
Director, Office of Antimicrobial Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

September 27, 2016

FDA's Patient-Focused Drug Development Initiative

Theresa Mullin, PhD
Director, Office of Strategic Programs
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

September 27, 2016

Patient-Focused Drug Development under PDUFA V

- **FDA is developing a more systematic way of gathering patient perspective on their condition and available treatment options**
  - Patient perspective helps inform our understanding of the context for the assessment of benefit-risk and decision making for new drugs
  - Input can inform FDA's oversight both during drug development and during our review of a marketing application

- **Patient-Focused Drug Development is part of FDA commitments under the fifth authorization of the Prescription Drug User Fee Act (PDUFA V)**
  - FDA will convene at least 20 meetings on specific disease areas in FY 2013-2017
  - Meetings will help develop a systematic approach to gathering patient input

Identifying Disease Areas for the Patient-Focused Meetings

- **FDA announced a preliminary set of diseases as potential meeting candidates**
  - Public input on these nominations was collected. FDA carefully considered these public comments and the perspectives of our drug review divisions at FDA

- **FDA identified a total of 24 diseases to be the focus of meetings for fiscal years 2013-2017**

Disease Areas to be the focus of meetings for FY 2013-2017

Fiscal Year 2013	Fiscal Year 2014	Fiscal Year 2015	Fiscal Year 2016-2017
• Chronic fatigue syndrome/ myalgic encephalomye litis • HIV • Lung cancer • Narcolepsy	• Sickle cell disease • Fibromyalgia • Pulmonary arterial hypertension • Inborn errors of metabolism • Hemophilia A, B, and other heritable bleeding disorders • Idiopathic pulmonary fibrosis	• Female sexual dysfunction • Breast cancer • Chagas disease • Functional gastrointestinal disorders • Huntington's disease and Parkinson's disease Alpha-1 antitrypsin deficiency	• Non-tuberculous mycobacterial lung infections • Psoriasis • Neuropathic pain associated with peripheral neuropathy • **Patients who have received an organ transplant** *To be announced* • Alopecia areata • Autism • Hereditary angioedema • Sarcopenia

Tailoring Each Patient-Focused Meeting

- **Each meeting focuses on a set of questions that aim to elicit patients' perspectives on their disease and on treatment approaches**
  - We start with a set of questions that could apply to any disease area; these questions are taken from FDA's benefit-risk framework and represent important considerations in our decision-making
  - We then further tailor the questions to the disease area of the meeting (e.g., current state of drug development, specific interests of the FDA review division, and the needs of the patient population)
- **Focus on relevant current topics in drug development for the disease at each meeting**
- **We've learned that active patient involvement and participation is key to the success of these meetings.**

"Voice of the Patient" Reports

- Following each meeting, FDA publishes a Voice of the Patient report that summarizes the patient testimony at the meeting, perspectives shared in written docket comments, as well as any unique views provided by those who joined the meeting webcast.

- These reports serve an important function in communicating to both FDA review staff and the regulated industry what improvements patients would most like to see in their daily life.

- FDA believes that the long run impact of this program will be a better, more informed understanding of how we might find ways to develop new treatments for these diseases.

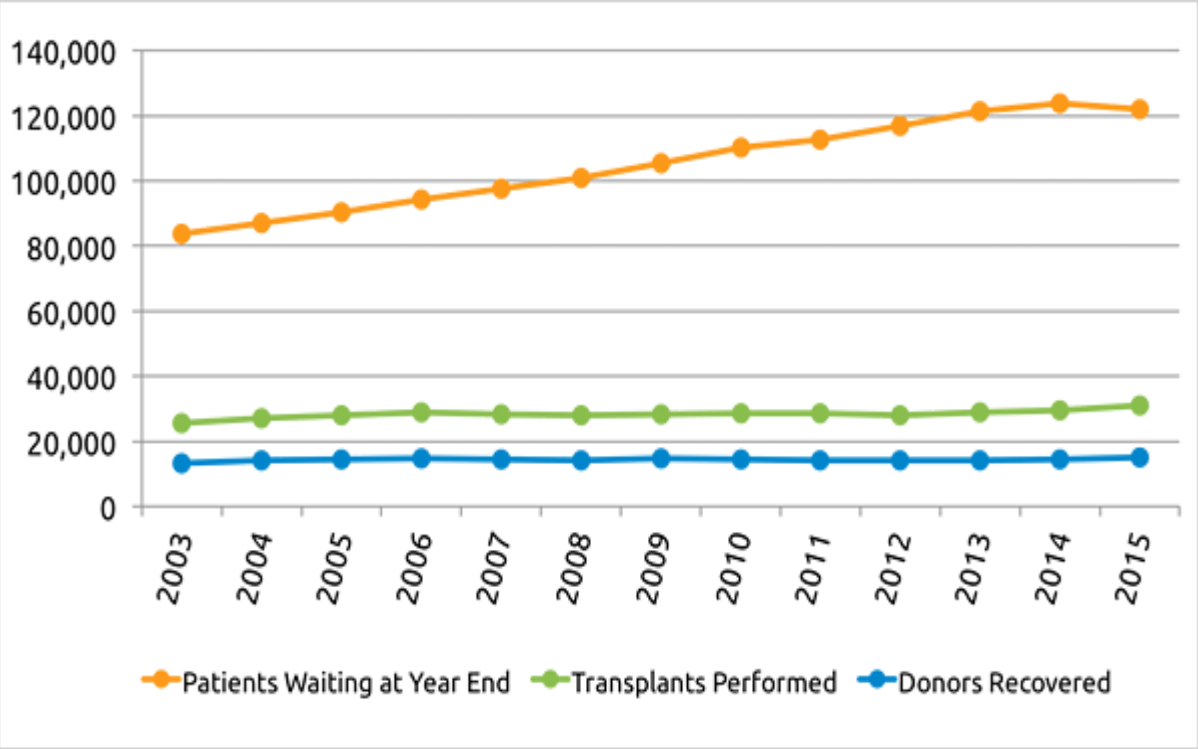
Overview of Organ Transplantation and Available Post-Transplant Treatment Options

Marc W. Cavaillé-Coll, MD, PhD
Medical Officer, Division of Transplant and Ophthalmology Products
Office of Antimicrobial Products
Office of New Drugs
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

September 27, 2016

Organ donation and transplantation to treat end-stage organ disease is life-saving for patients with a serious condition

The number of patients on the waiting list is growing faster than the number of donors recovered and transplants performed.



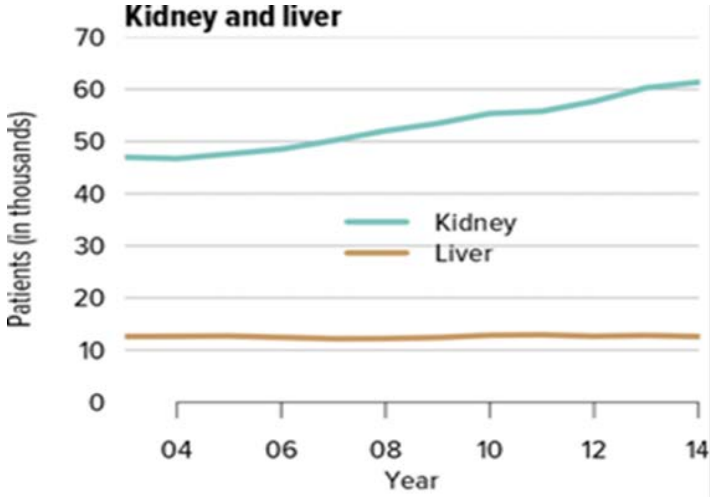
Allocation of Organs in the US

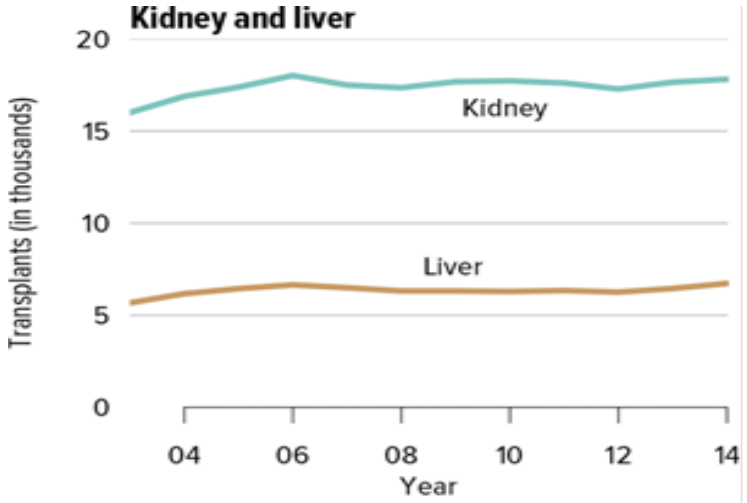
- National Organ Transplant Act (NOTA) of 1984
- Organ Procurement and Transplantation Network (OPTN)
- Organ procurement organizations (OPOs)
- United Network for Organ Sharing (UNOS)
- Scientific Registry of Transplant Recipients (SRTR)

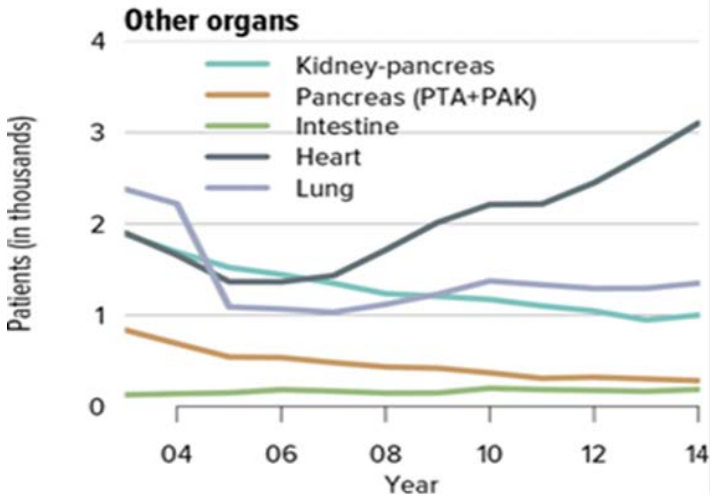
Types of organs transplanted annually in the US

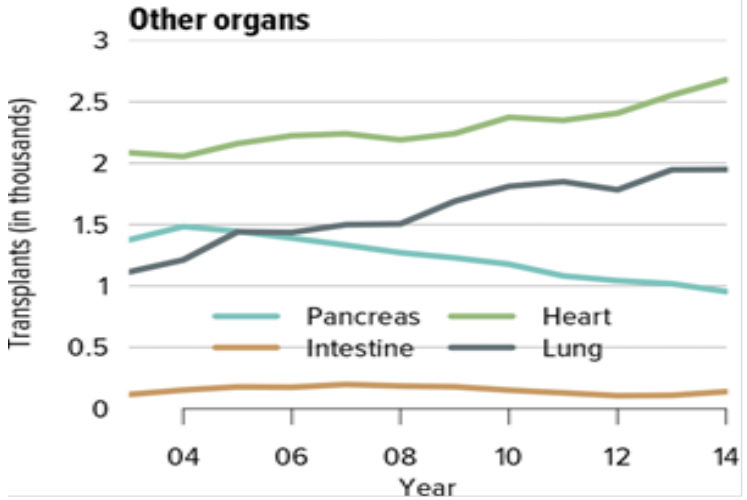
- Kidney (deceased-donor and living-donor)
- Liver (deceased-donor and living-donor)
- Pancreas (deceased-donor only)
- Intestine (deceased-donor and living-donor)
- Heart (deceased-donor only)
- Lung (deceased-donor and living-related lung transplantation)
- Heart/Lung (deceased-donor and domino transplant)

Patients active on the waiting list (left) and Total transplants, (right) 2004-2014









Medications used in Organ Transplantation: Polypharmacy is the Rule

- **Prevention/treatment of rejection**
  - Induction immunosuppression (intensive combination regimens)
  - Maintenance immunosuppression (less intensive combination regimens)
  - Treatment of acute rejection
- **Prevention/treatment of infection** (i.e. viral, bacterial, fungal and other opportunistic infections)
- **Treatment of underlying medical conditions** (i.e. hypertension, diabetes, hepatitis C)
- **Treatment of emergent complications** of immunosuppressive regimen (i.e. hypertension, new onset diabetes etc.)

Treatment Options: Immunosuppression in use in transplantation

Immunosuppression in Organ Transplantation

Agents used for Induction Treatment

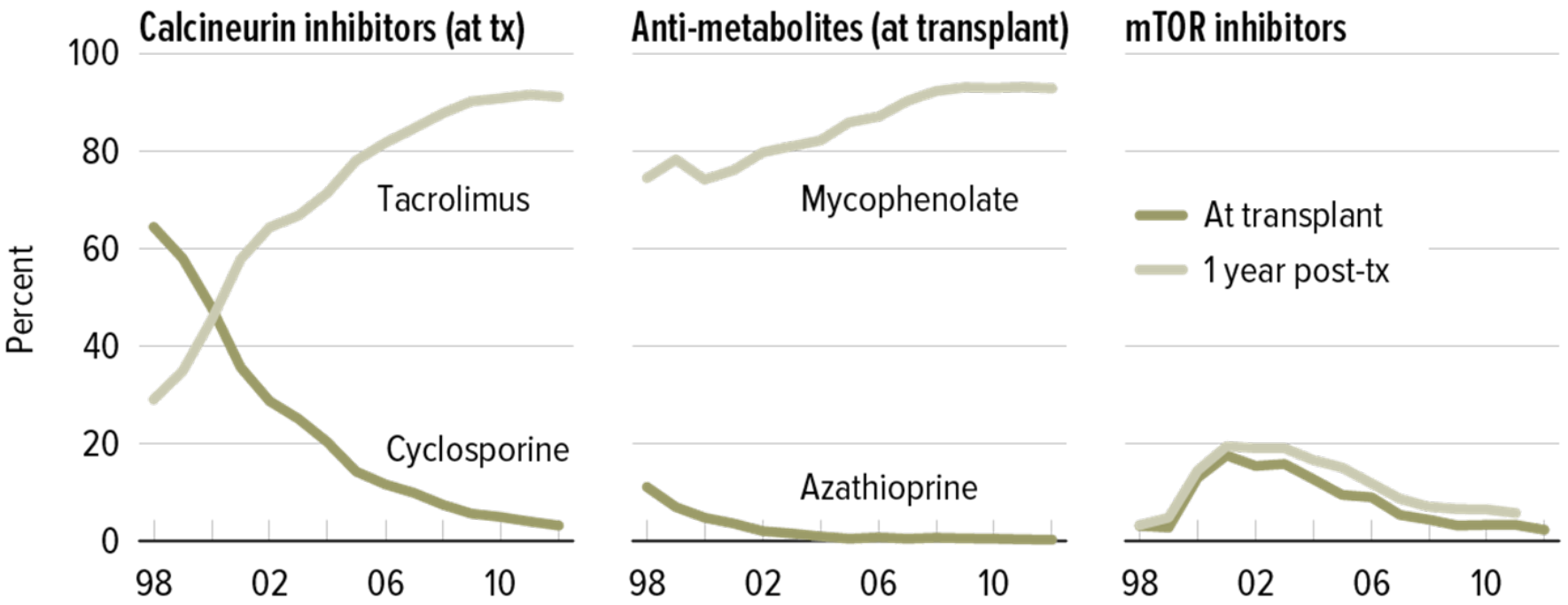
- Lymphocyte depleting agents - Polyclonal IgG antibodies derived from horse (lymphocyte immune globulin) or rabbit (antithymocyte globulin)
- Interleukin-2 receptor antagonists (IL-2RA) – Monoclonal antibodies modified to be humanized or chimeric antibodies that bind to the α chain of the interleukin 2 receptor on T cells and thereby impair lymphocyte proliferation.
- High dose use of agents also used for maintenance immunosuppression.

Immunosuppression in Organ Transplantation

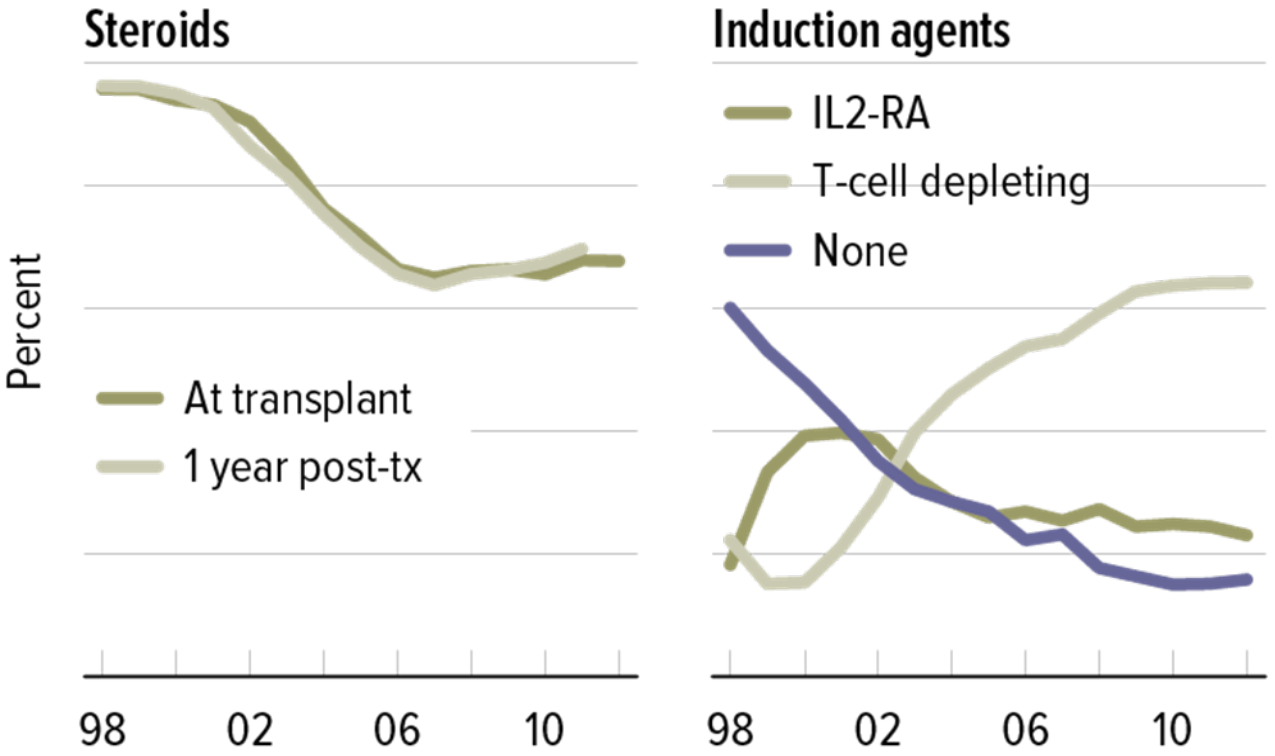
Maintenance Immunosuppression (Combination of 2 or 3 agents)

- Glucocorticoids are used both for induction and maintenance immunosuppression as well as for treatment of rejection.
- Calcineurin inhibitors include cyclosporine and tacrolimus around which additional agents are added to complete the immunosuppressive regimen.
- Purine antagonists include azathioprine, mycophenolate mofetil and mycophenolic acid, which act by different molecular mechanisms resulting in inhibition of T and B cell proliferation.
- Mammalian target of rapamycin inhibitors (mTORi) include sirolimus and everolimus which bind to the same immunophilin as tacrolimus and modulate mTOR, resulting in cell arrest in the G1-S phase.
- Selective T-cell costimulation blocker belatacept is a soluble fusion protein that binds to CD-80 and CD86 on antigen-presenting cells thereby blocking CD28 costimulation of T lymphocytes.

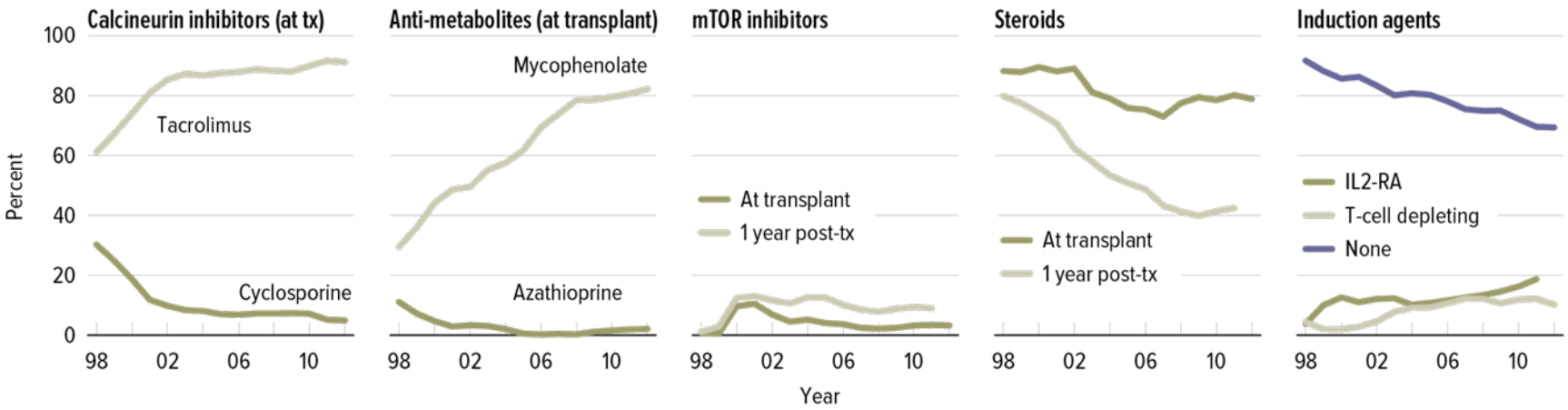
Immunosuppression use in adult kidney transplant recipients by year *[SRTR & OPTN Annual Data Report, 2012 KI 4.7]*



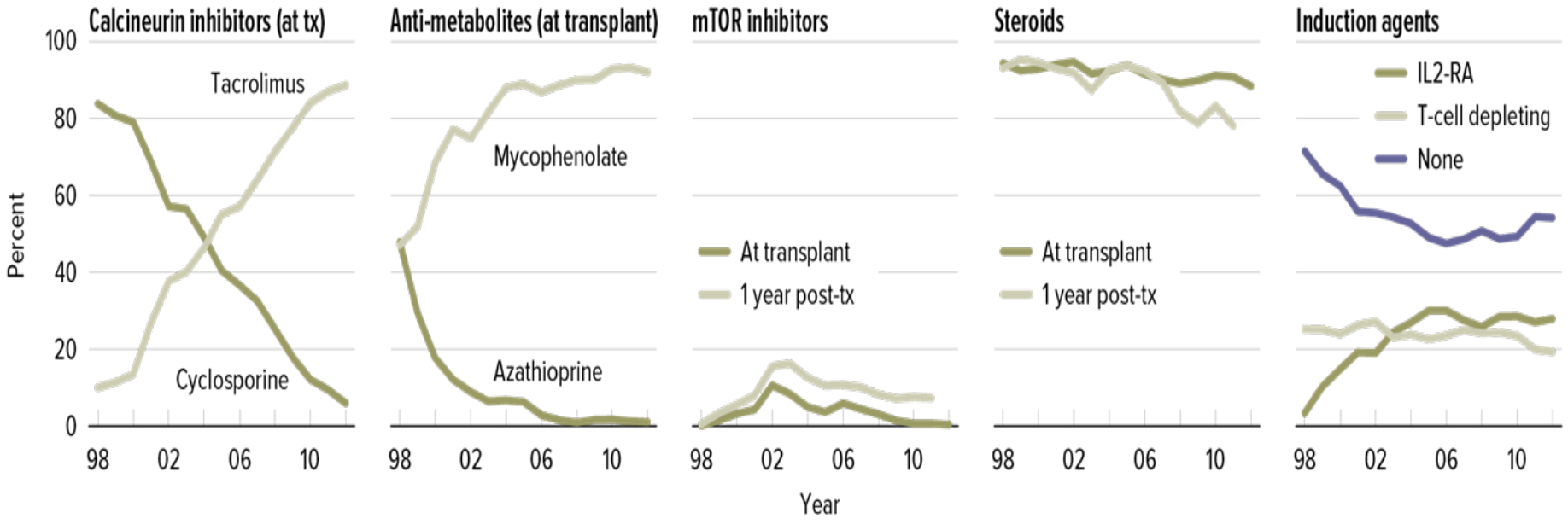
Immunosuppression use in adult kidney transplant recipients by year *[SRTR & OPTN Annual Data Report, 2012 KI 4.7]* cont'd



Immunosuppression use in adult liver transplant recipients by year *[SRTR & OPTN Annual Data Report, 2012 LI 4.8]*



Immunosuppression use in adult heart transplant recipients by year *[SRTR & OPTN Annual Data Report, 2012 HR 3.7]*



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Outcomes

Outcomes from SRTR/OPTN 2015 in AJT 2016

- Five–year graft survival rates were 73.5% for deceased donor kidney transplants and 85.7% for living donor transplants.
- For patients who underwent liver transplant in 2009, the 5-year overall graft survival rate was 70.1%. As of June 30, 2014, 71,699 liver transplant recipients were alive with a functioning graft, with many more pediatric recipients reaching adulthood each year.
- For patients who underwent heart transplantation from 2007 through 2009 5-year survival was 75.9%. On June 30, 2014, 28,110 heart transplant recipients were alive with functioning graft; most had undergone transplant at the age of 50 years or older.

Outcomes from SRTR/OPTN 2015 in AJT 2016

- A total of 1949 lung transplants were performed in 2014, including adult and pediatric recipients. Among recipients who underwent lung transplantation in 2007-2009, overall 5-year unadjusted patient survival was 54.4%.
- Graft survival in intestine transplants has improved over the past decade. The number of recipients alive with a functioning intestine graft has steadily increased since 2003, to 1056 in 2014; 42.5% were pediatric intestine liver transplant recipients.
- The number of pancreas transplants has declined since 2004.

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Future Challenges

New approaches are needed:

- To increase organ donation procurement and decrease discard of procured organs
- To prevent/treat delayed graft function
- To prevent/treat antibody-mediated rejection
- To individualize treatment (biomarkers, genomics, systems biology)
- To induce durable stable immune tolerance
- To minimize adverse reactions associated with the IS regimens
- To integrate use of novel concomitant agents and manage drug interactions

The risk/benefit of new/old approaches and interventions need to be assessed from a patient's perspective.

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Thank You

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The Road from Patient-Focused Drug Development Public Meetings to Clinical Study Endpoints

Michelle Campbell, PhD
Clinical Outcome Assessments Staff
Office of New Drugs
Center for Drug Evaluation and Research

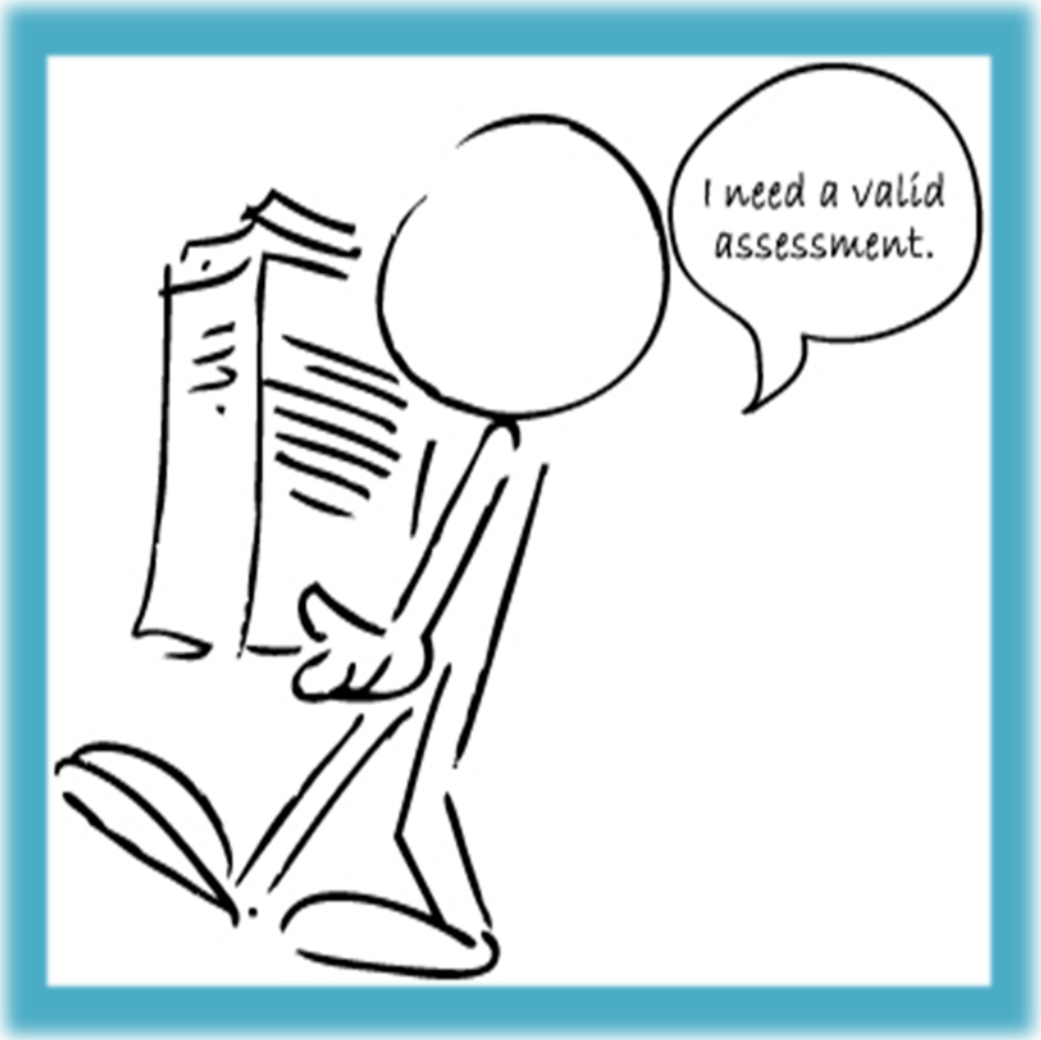
Disclaimer

The views expressed in this presentation are those of the speaker, and do not necessarily represent an official FDA position.

PATIENT-FOCUSED DRUG DEVELOPMENT (PFDD) MEETINGS

WHERE DO WE GO FROM HERE


PATIENTS' VOICE


I need a valid assessment.

Two Pathways for FDA Clinical Outcome Assessment Review & Advice

1

Within an individual drug development program

- Investigational New Drug (IND) submissions to FDA
- Potential to result in labeling claims

2

Within the Drug Development Tool (DDT) qualification program; **outside** of an individual drug development program

- Potential to result in qualification*

Key Takeaways

- PFDD meetings are a “starting point” for developing patient-focused outcome measures and endpoints
- The outcomes of PFDD meetings will support and guide FDA risk-benefit assessments in drug reviews
- Patients’ input ultimately helps determine:
  - WHAT is measured to provide evidence of treatment benefit
  - HOW best to measure concepts in a clinical study
  - WHAT a meaningful improvement is in treatment benefit

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Overview of Discussion Format

Sara Eggers, PhD
Office of Strategic Programs
Center for Drug Evaluation
Food and Drug Administration

September 27, 2016

Discussion Overview

Topic 1 Discussion

- The most significant changes in your overall health since you received your transplanted organ
- Symptoms related to your organ transplant and post-transplant effects that have the most significant impact on your life
- What worries you most about your health post-transplant

Topic 2 Discussion

- What you are currently doing to manage your health post-transplant
- How well your treatments manage your most significant symptoms
- The most burdensome downsides to your treatments
- Specific things you would look for in an ideal treatment

Discussion Format

- **We will first hear from a panel of patients**
  - The purpose is to set a good foundation for our discussion
  - They reflect a range of experiences with organ transplantation

- **We will then broaden the dialogue to include patients in the audience**
  - The purpose is to build on the experiences shared by the panel
  - We will ask questions and invite you to raise your hand to respond
  - Please state your name before answering

Discussion Format, continued

- **You'll have a chance to answer "polling" questions**
  - Their purpose is to aid our discussion
  - In-person participants, use the "clickers" to respond
  - Web participants, answer the questions through the webcast
  - Patients or parents of patients only, please

- **Web participants can add comments through the webcast**
  - Although they may not all be read or summarized today, your comments will be incorporated into our summary report
  - We'll occasionally go to the phones to give you another opportunity to contribute

Resources at FDA

- FDA Office of Health and Constituent Affairs
  - Contact: PatientNetwork@fda.hhs.gov, (301) 796-8460
  - Liaison between FDA and stakeholder organizations
  - Runs the Patient Representative Program
    - Patient Representatives advise FDA at Advisory Committee meetings

- CDER Office of Center Director
  - Professional Affairs and Stakeholder Engagement (PASE)
  - Contact: Christopher Melton, christopher.melton@fda.hhs.gov
  - Facilitates communication and collaboration between CDER and patient and healthcare professional stakeholders and others on issues concerning drug development, drug review and drug safety.

Discussion Ground Rules

- We encourage patients to contribute to the dialogue– caregivers and advocates are welcome too
- FDA is here to listen
- Discussion will focus on health effects and treatments
  - Open Public Comment Period is available to comment on other topics
- The views expressed today are personal opinions
- Respect for one another is paramount
- Let us know how the meeting went today; evaluation forms are available at the registration table

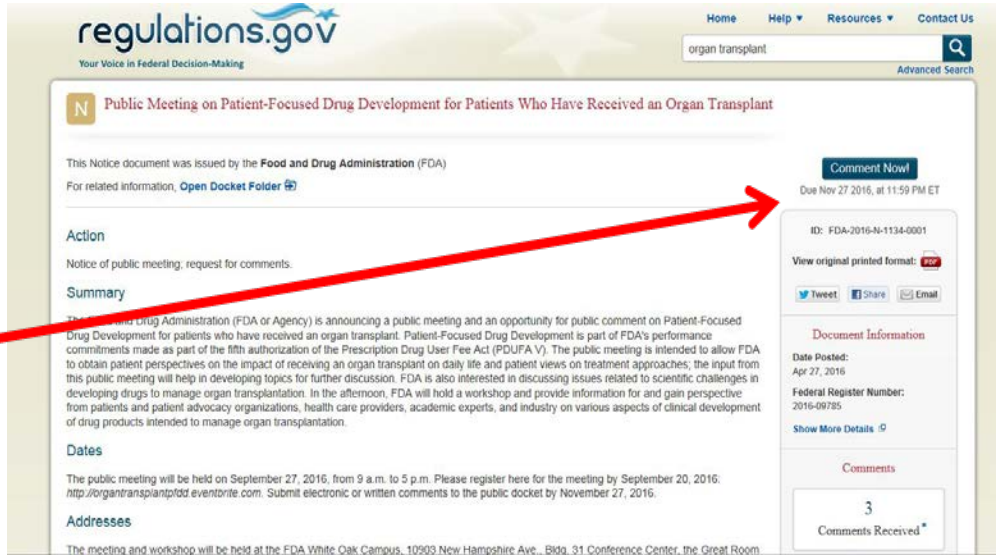
Send us your comments!

- **You can send us comments through the "public docket"**
  - The docket will be open until November 27, 2016
  - Share your experience, or expand upon something discussed today
  - Comments will be incorporated into our summary report
  - Anyone is welcome to comment

Visit:
https://www.regulations.gov/document?D=FDA-2016-N-1134-0001

Or Search "Organ Transplant" on
www.regulations.gov

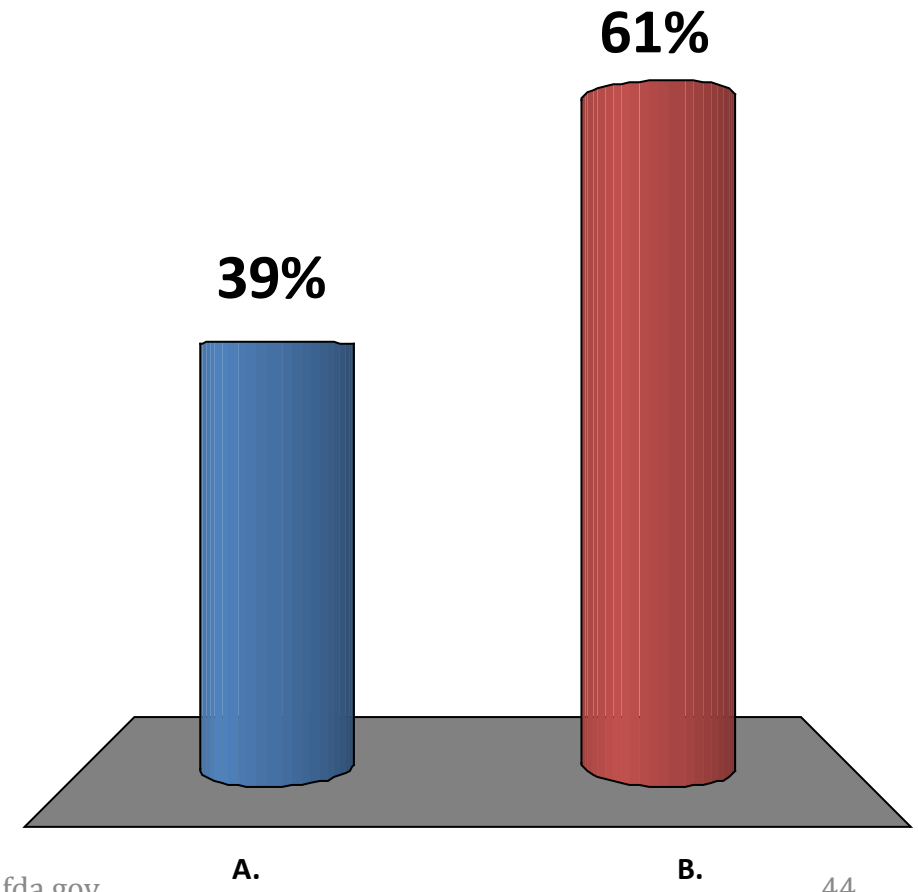
And **Click Comment Now!**



Where do you live?

A. Within Washington, DC metropolitan area (including the Virginia and Maryland suburbs)

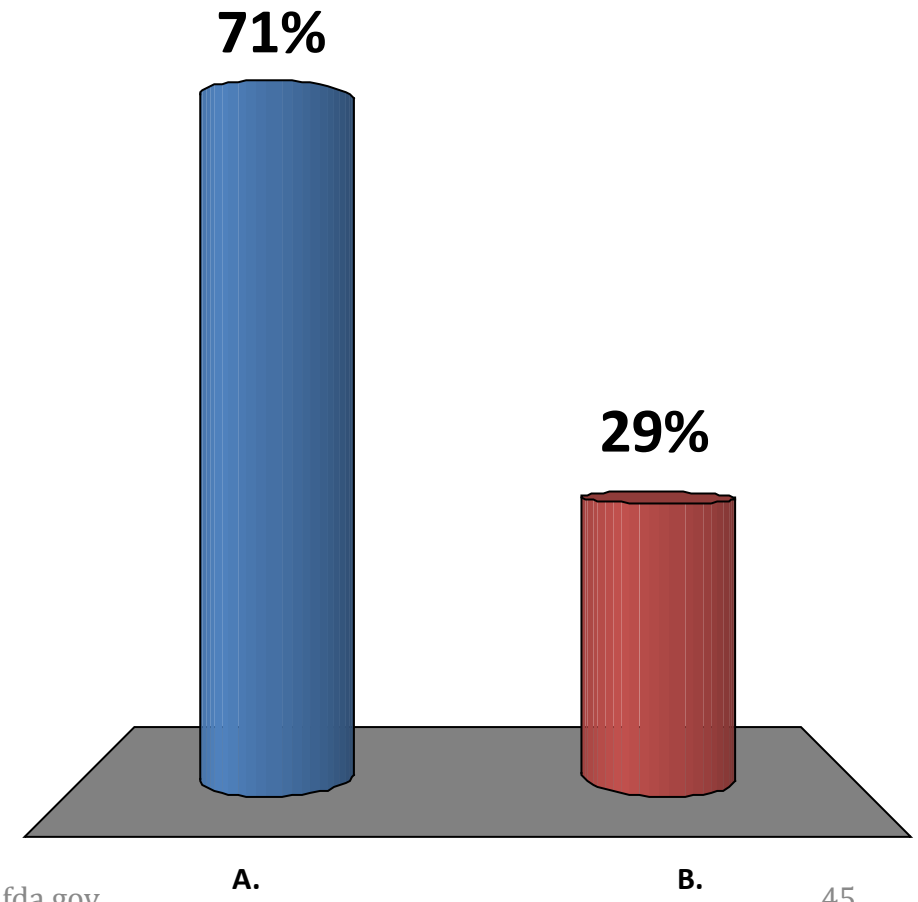
B. Outside of the Washington, D.C. metropolitan area



Have you received an organ transplant?

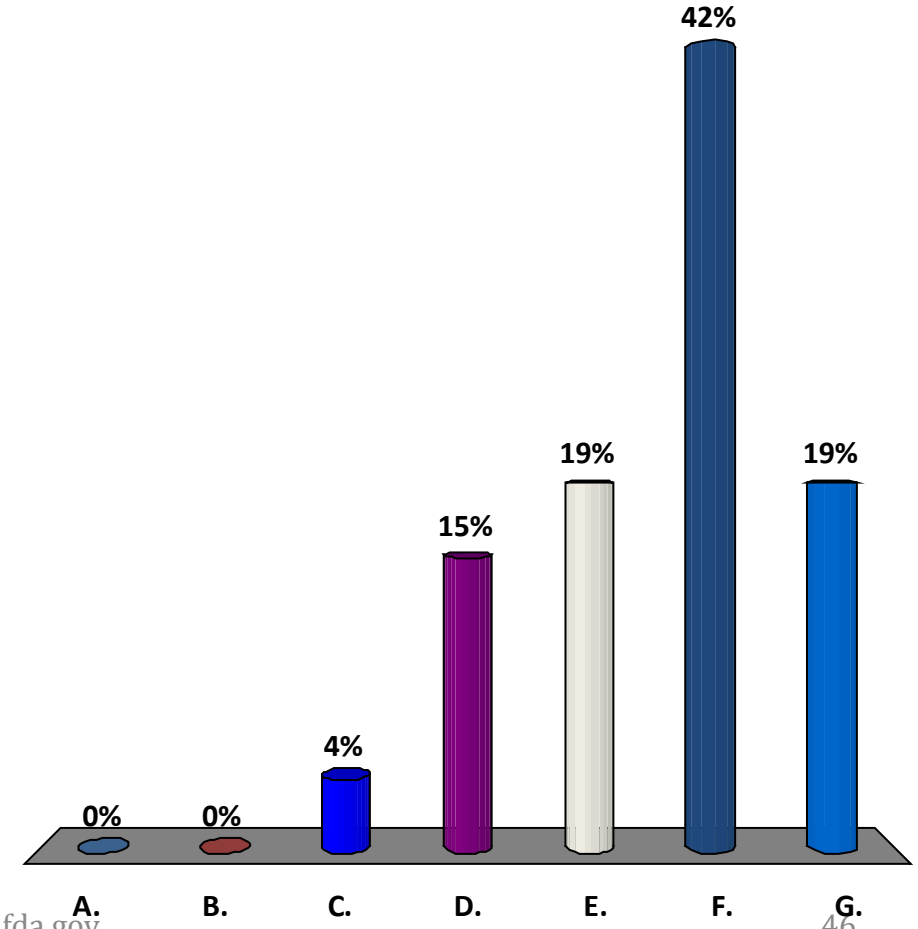
A. Yes

B. No



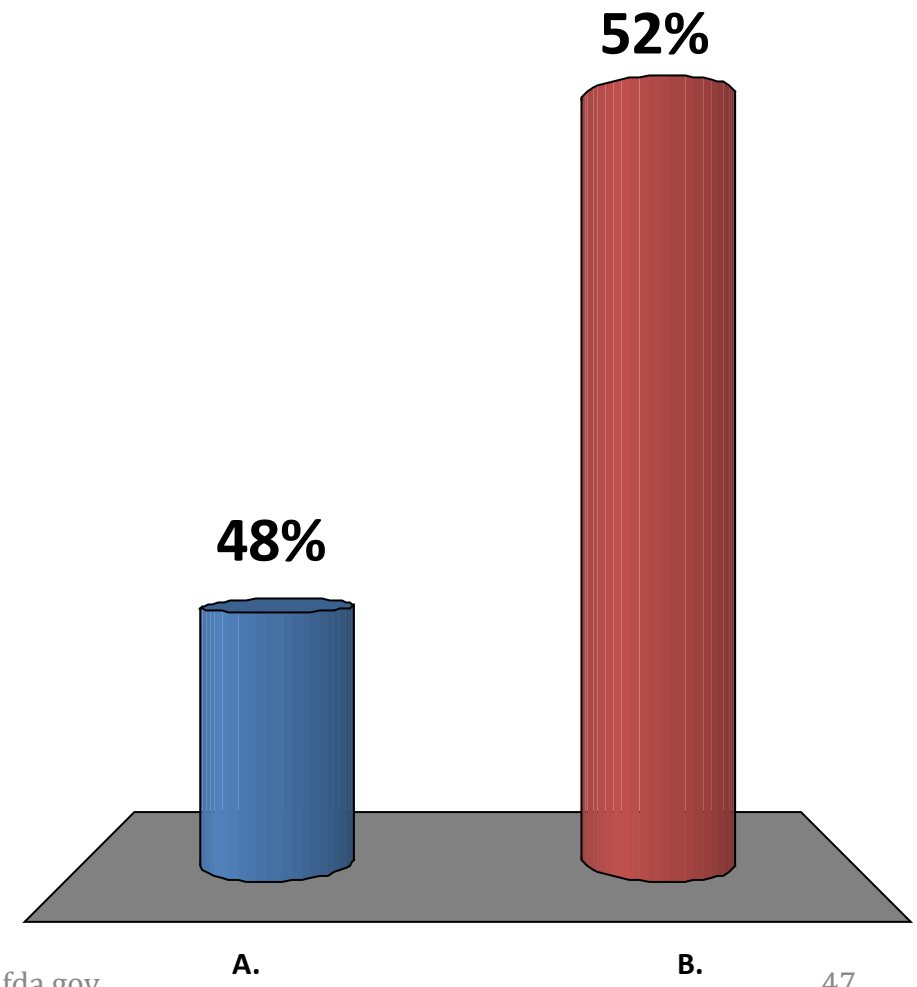
What is you or your loved one's age?

A. < 1
B. 1 – 10
C. 11 – 17
D. 18 – 34
E. 35 – 49
F. 50 – 64
G. 65 or greater



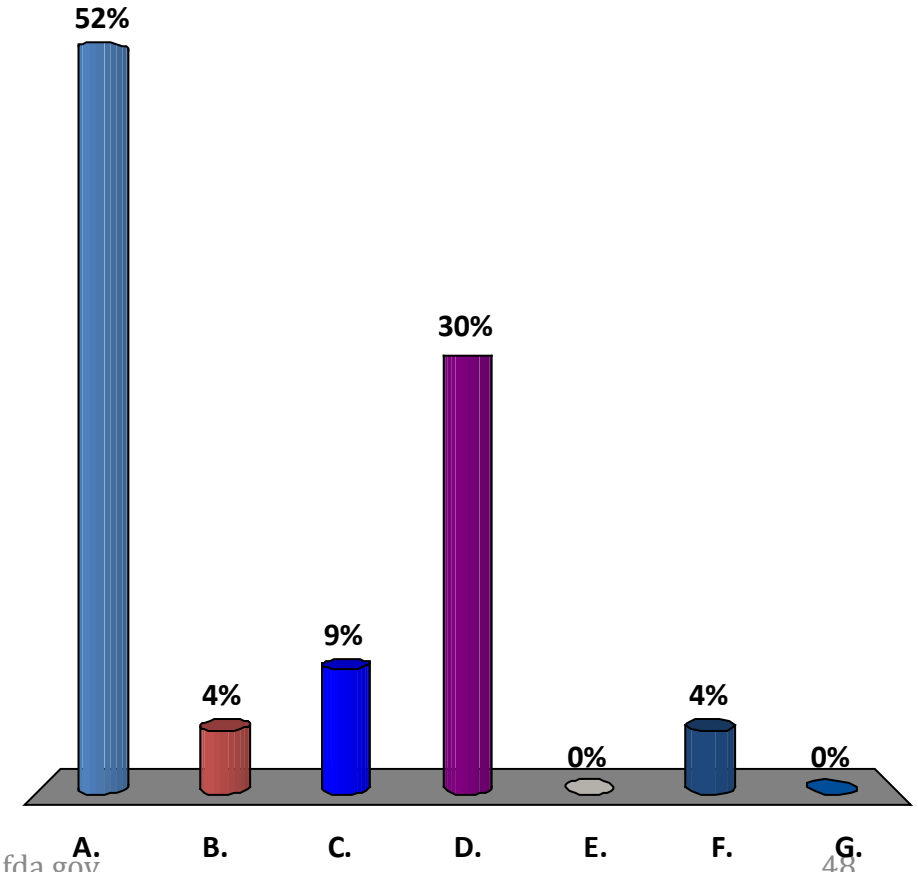
Do you identify as:

A. Male
B. Female



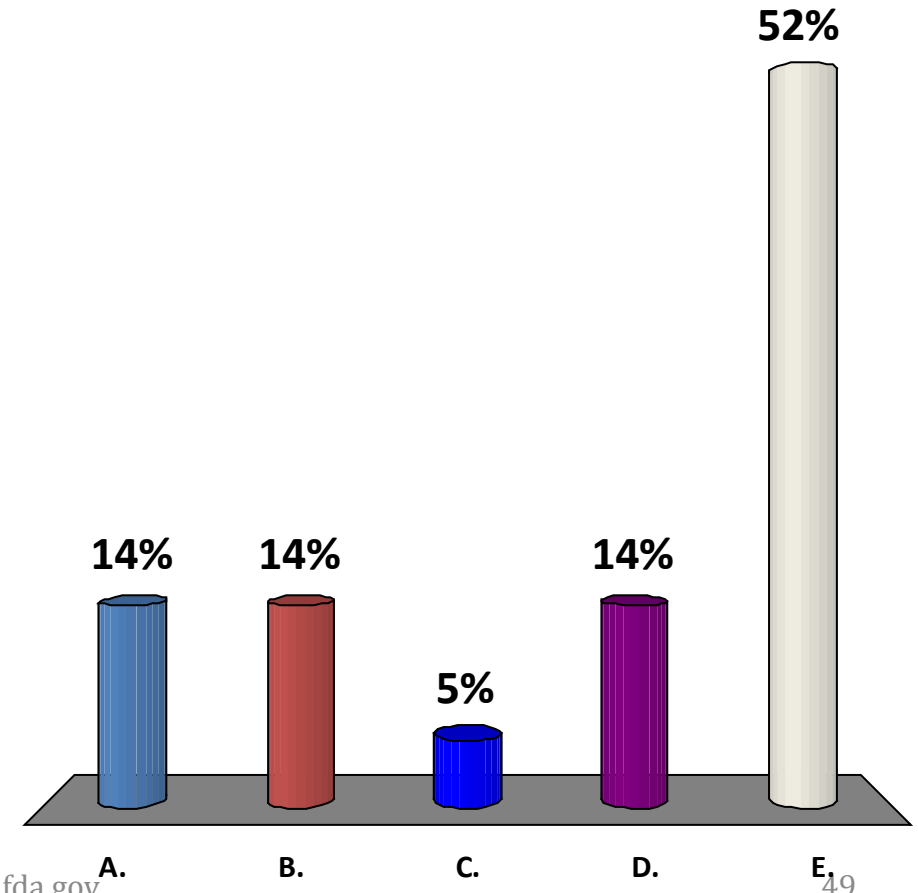
What type of organ transplant have you received ?

A. Kidney
B. Heart
C. Liver
D. Lung
E. Pancreas
F. Multiple different organs
G. Others not mentioned



What is the length of time since you received an organ transplant?

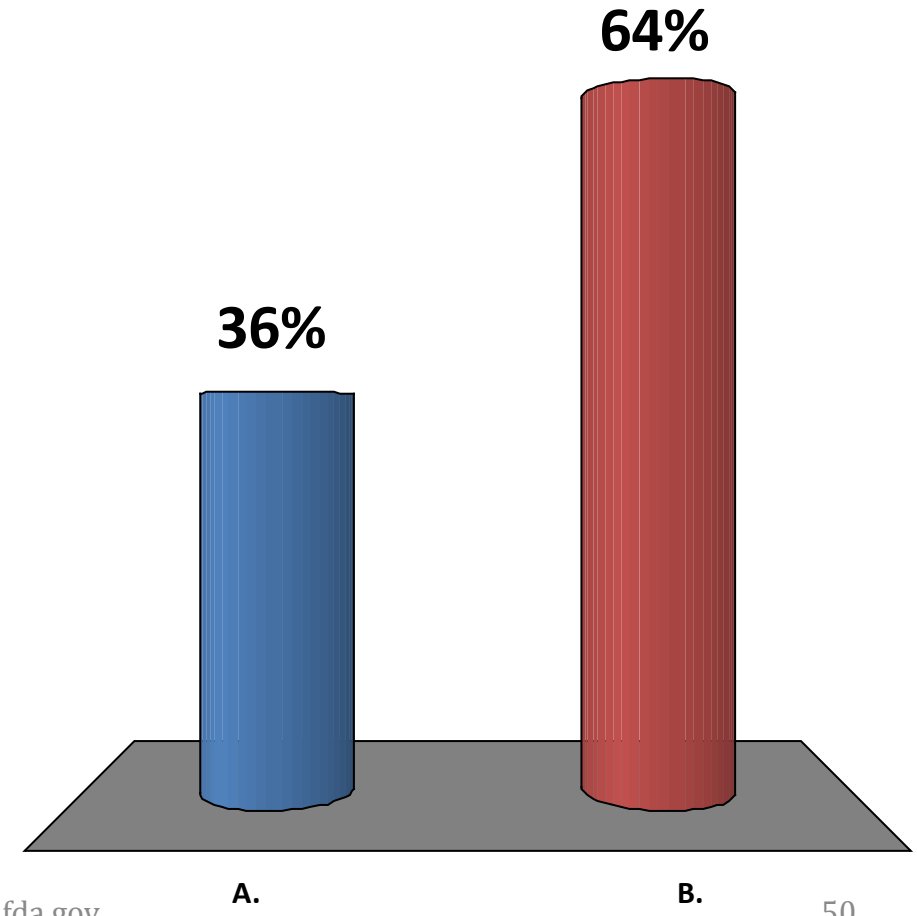
A. Less than 1 year ago
B. 1 – 2 years ago
C. 3 – 5 years ago
D. 6 – 10 years ago
E. Greater than 10 years ago



Have you received more than one organ transplant (or retransplant)?

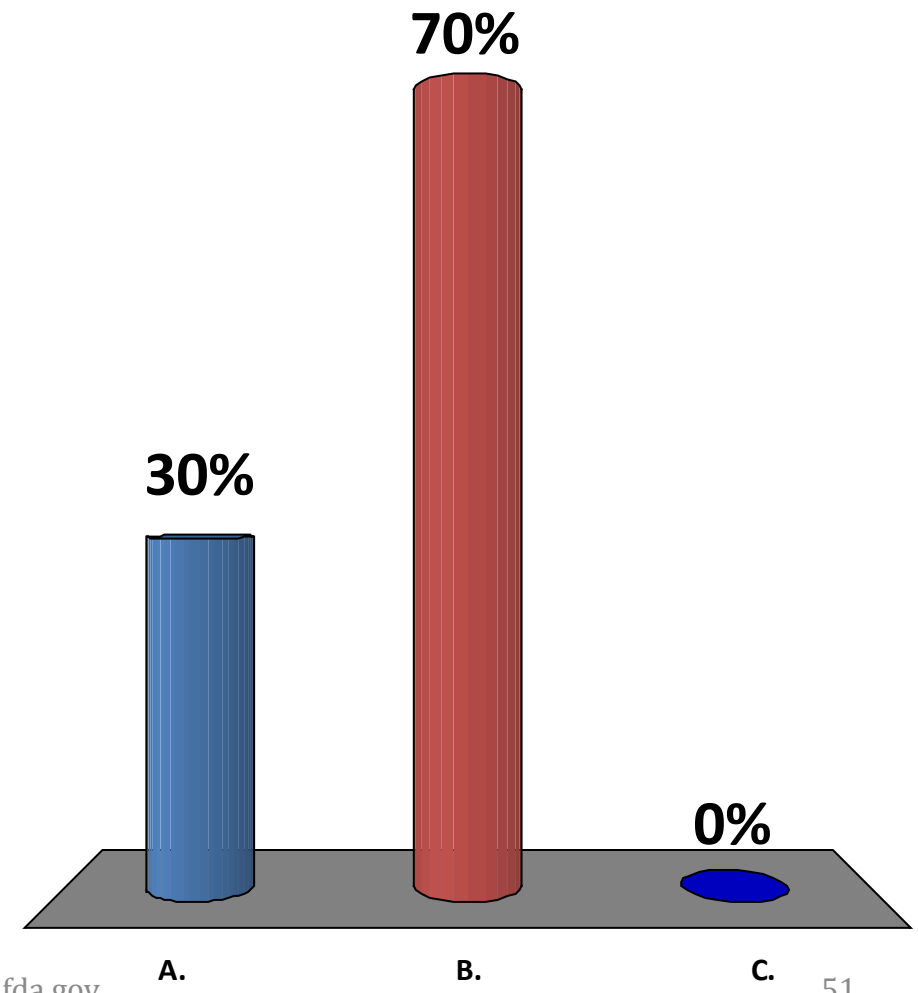
A. Yes

B. No



Did you receive your organ transplant from a living or deceased donor?

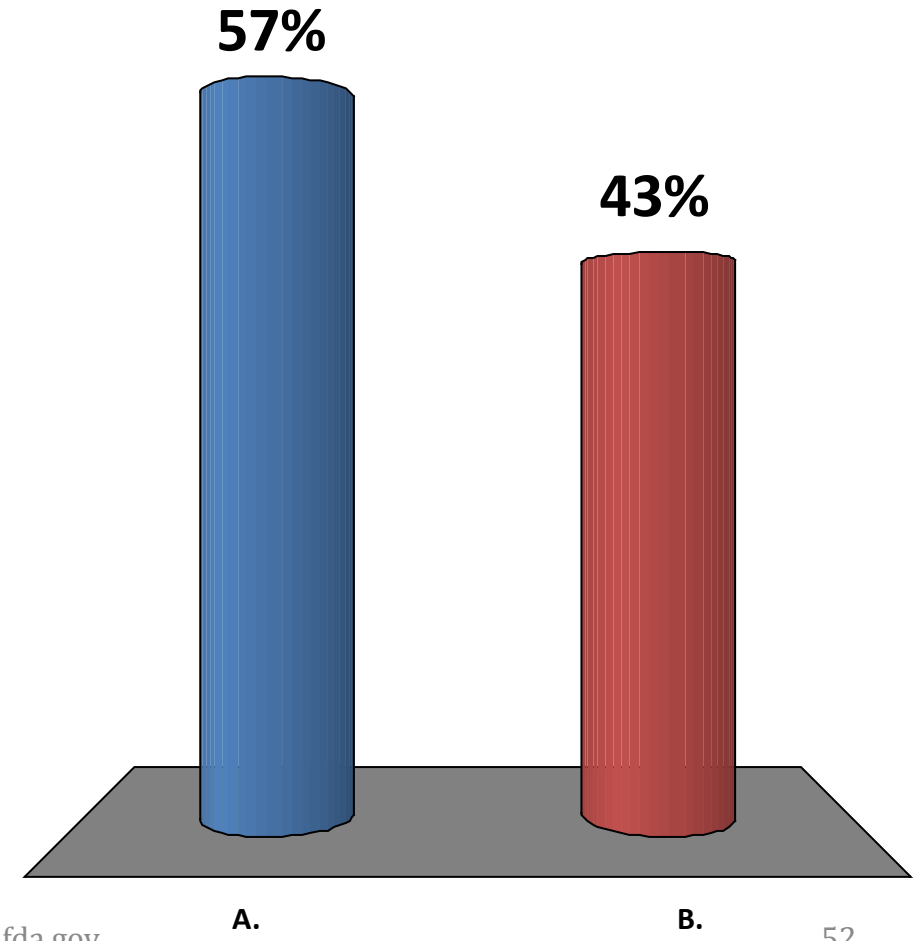
A. Living donor
B. Deceased donor
C. I don't know



Have you experienced organ rejection?

A. Yes

B. No



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Topic 1 Discussion

Sara Eggers & Meghana Chalasani

Facilitator

Topic 1 Panel Participants

- Lindsey Duquette
- Jim Gleason
- Jeffrey Goldstein
- Michael Garrett
- Leilah Sampson

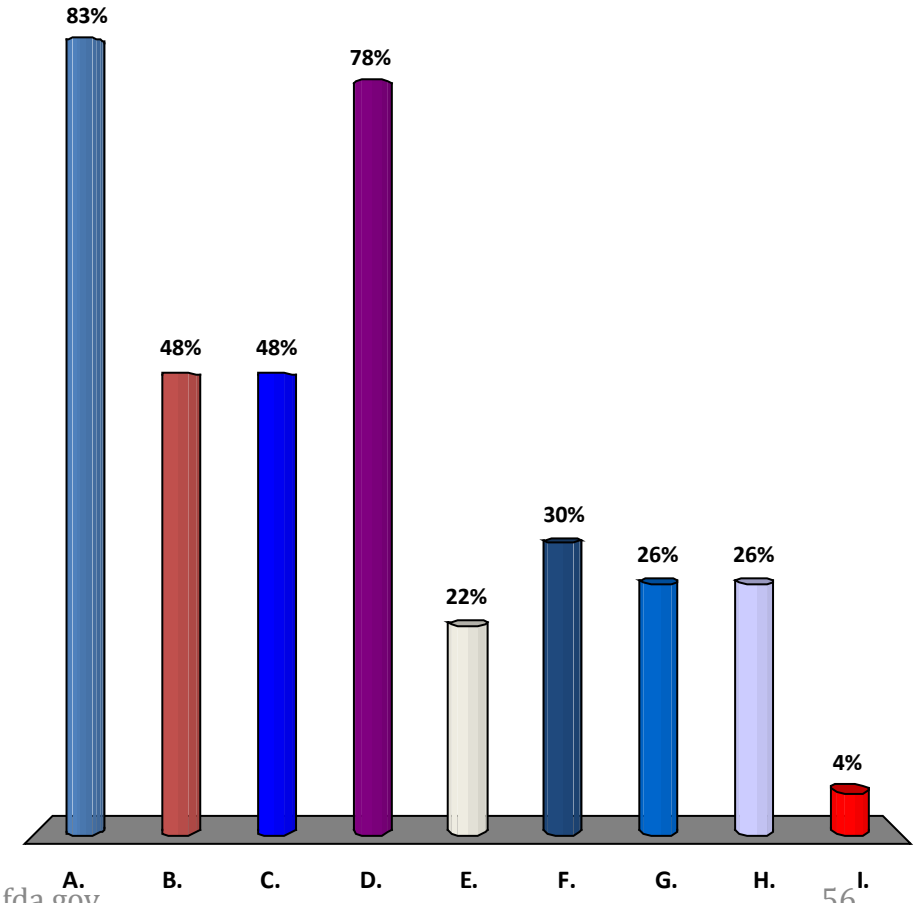
Topic 1 Discussion

- What have been the most significant changes in your overall health since you received your transplanted organ? How long has it been since you received your transplant?
- Focusing on symptoms related to your organ transplant and post-transplant effects, which 1-3 symptoms have the most significant impact on your life?
- Are there specific activities that are important to you but that you cannot do at all or as fully as you would like because of your transplant?
- How do your symptoms and their negative impacts affect your daily life on the best days? On the worst days?
- How has your experience with your transplanted organ changed over time? Do particular symptoms come and go as your duration of time with a transplanted organ has increased? If so, do you know of anything that makes your symptoms better? Worse?
- What worries you most about your health post-transplant?

What comorbid condition(s) have you experienced post-transplantation (if applicable)?

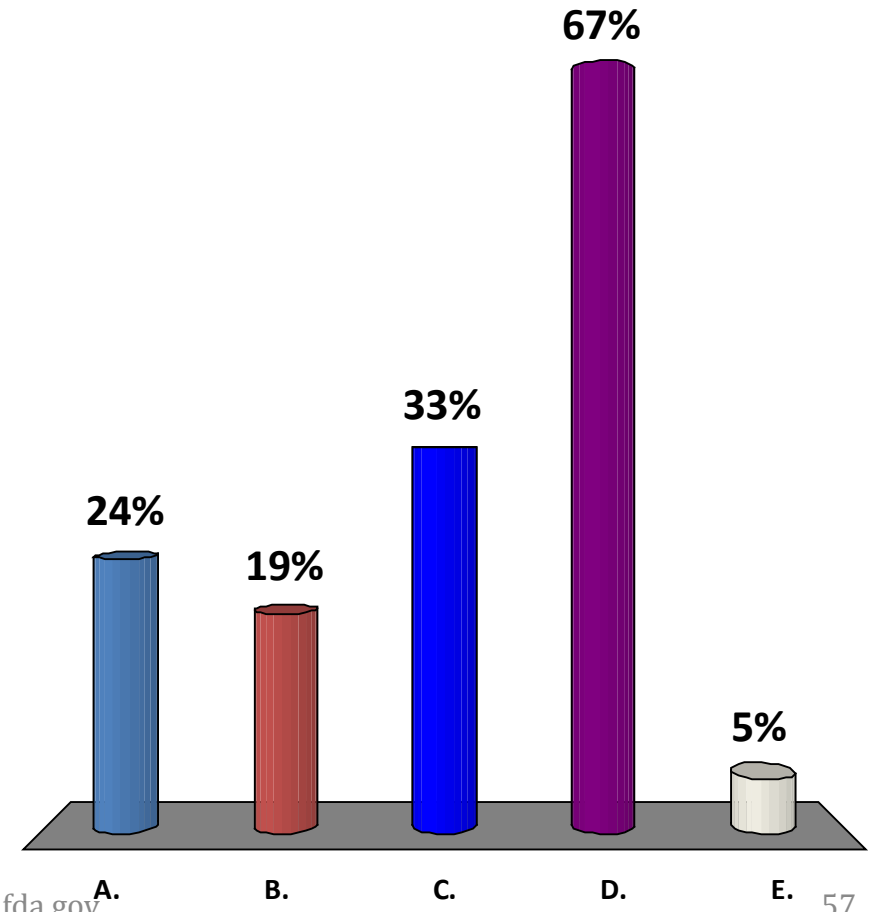
Check all that apply

A. Bacterial (such as urinary tract infection, respiratory infection) or viral infection (such as cytomegalovirus(CMV), Epstein-Barr Virus (EBV), BK virus)
B. Cancer
C. Cardiovascular Disease (such as high blood pressure, coronary artery disease, heart failure)
D. Depression or anxiety
E. Diabetes
F. Fungal (such as candidiasis, aspergillosis) or parasitic infection
G. Kidney disease
H. Other comorbid condition(s) not mentioned
I. I do not have any comorbid conditions that I am aware of



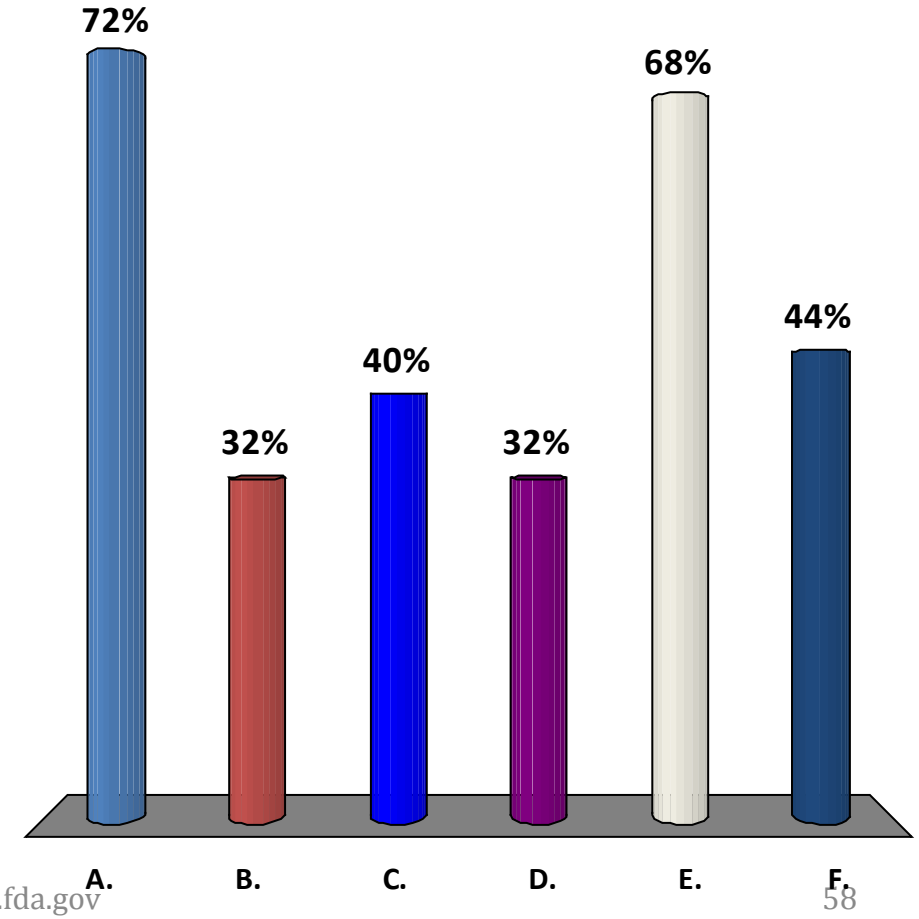
Based on your response previously, which statement best categorizes the source of your comorbidity? Check all that apply.

A. The comorbidity I experienced was transmitted from the donor of my organ transplant (i.e donor-derived).
B. The comorbidity I experienced was present prior to my organ transplantation (i.e recipient-derived).
C. The comorbidity I experienced was acquired in a community setting due to immunosuppression or infection.
D. The comorbidity I experienced was acquired as an adverse effect of my post transplantation therapy regimen.
E. Other areas not mentioned



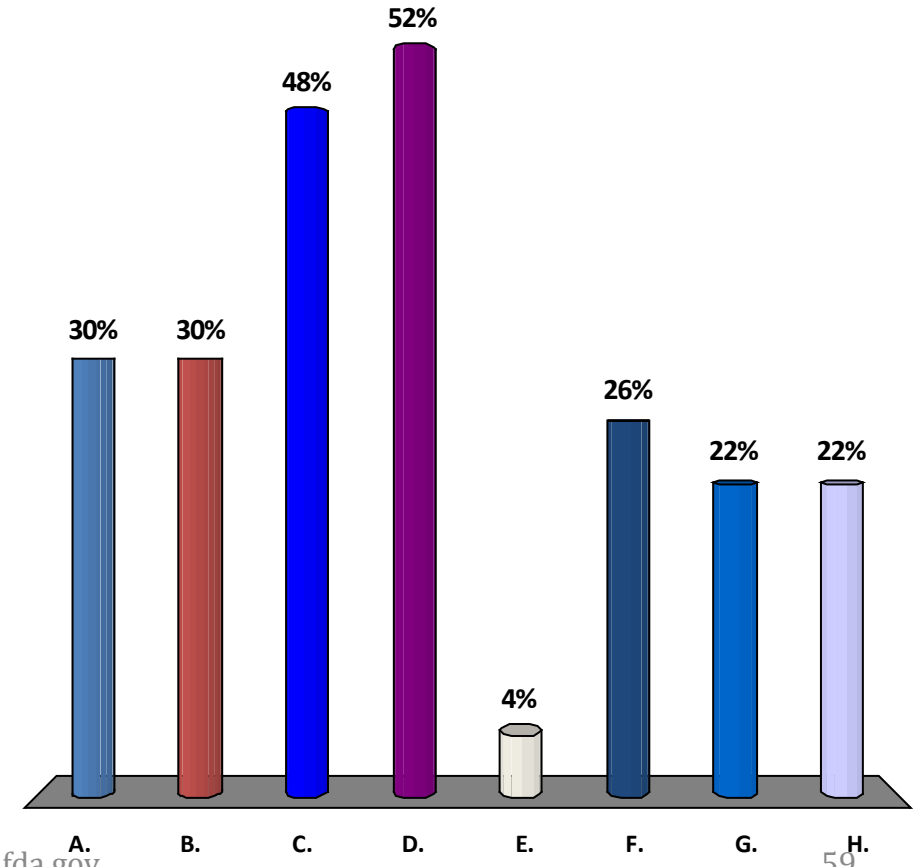
Post-transplantation, which aspects of your personal care have changed most significantly? Check all that apply.

A. Skin Care (such as reduced exposure to light, risk of cancer)
B. Hair Care (due hair loss, increased hair growth)
C. Dental Care (such as tooth or gum pain)
D. Eye Care (such as vision changes, cataracts)
E. Dietary Needs (due to constipation, diarrhea, or weight gain/loss)
F. Other areas not mentioned



What are the most bothersome impacts of your organ transplantation on your daily life? Please choose up to three impacts.

A. Ability to participate in or perform activities (such as work, participation in sports or social activities, driving, make or keep plans for activities)
B. Ability to fall asleep at night
C. Ability to sleep through the night
D. Ability to concentrate or stay focused
E. Ability to care for self, family, and others
F. Impacts on sexual intimacy
G. Emotional impacts (such as fear, hopelessness)
H. Other impacts not mentioned



BREAK

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Topic 2 Discussion

Sara Eggers & Meghana Chalasani
Facilitator

Topic 2 Panel Participants

- Piper Beatty
- Dan Bonner
- Deborah Heffernan
- Jack Lennon
- Roberta Wager

Topic 2 Discussion

- What are you currently doing to maintain your transplanted organ or treat related health concerns following transplantation? How has your post-transplant treatment regimen changed over time, and why?

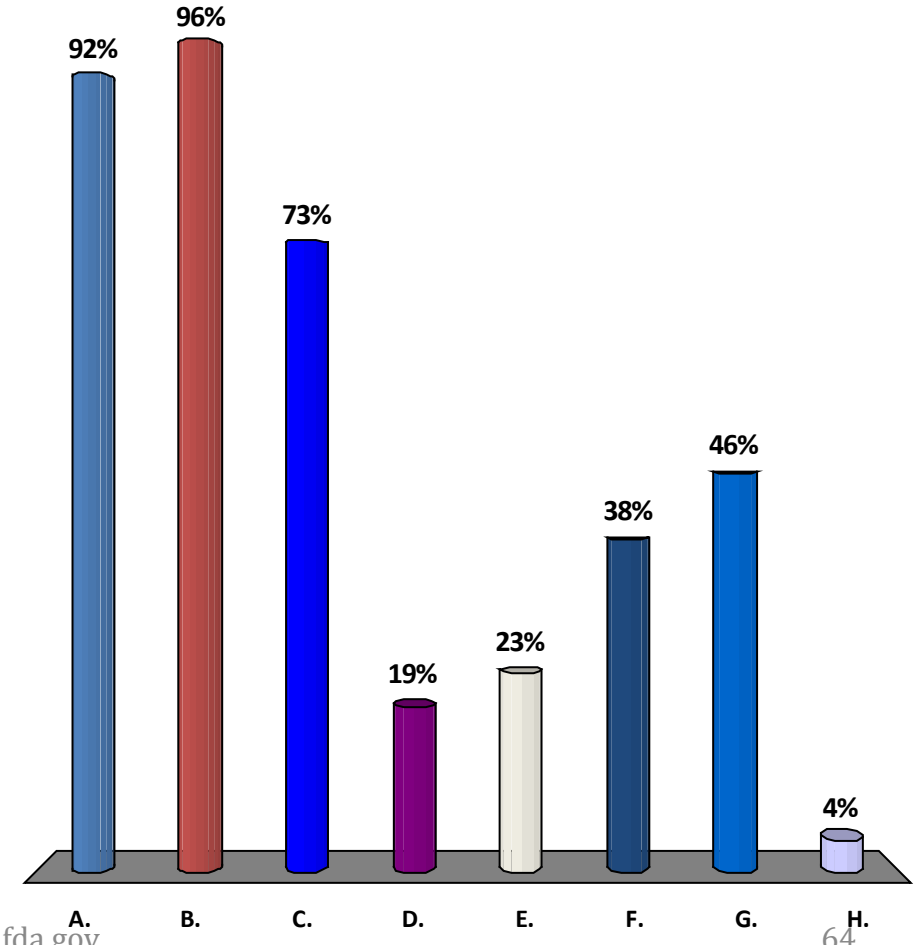
- How well does your current treatment regimen manage the most significant symptoms you experience post-transplantation?

- What are the most significant downsides to your current treatments, and how do they affect your daily life? What are the biggest challenges you face in maintaining your post-transplant treatment regimen?

- What specific things would you look for in an ideal treatment for managing your transplanted organ?

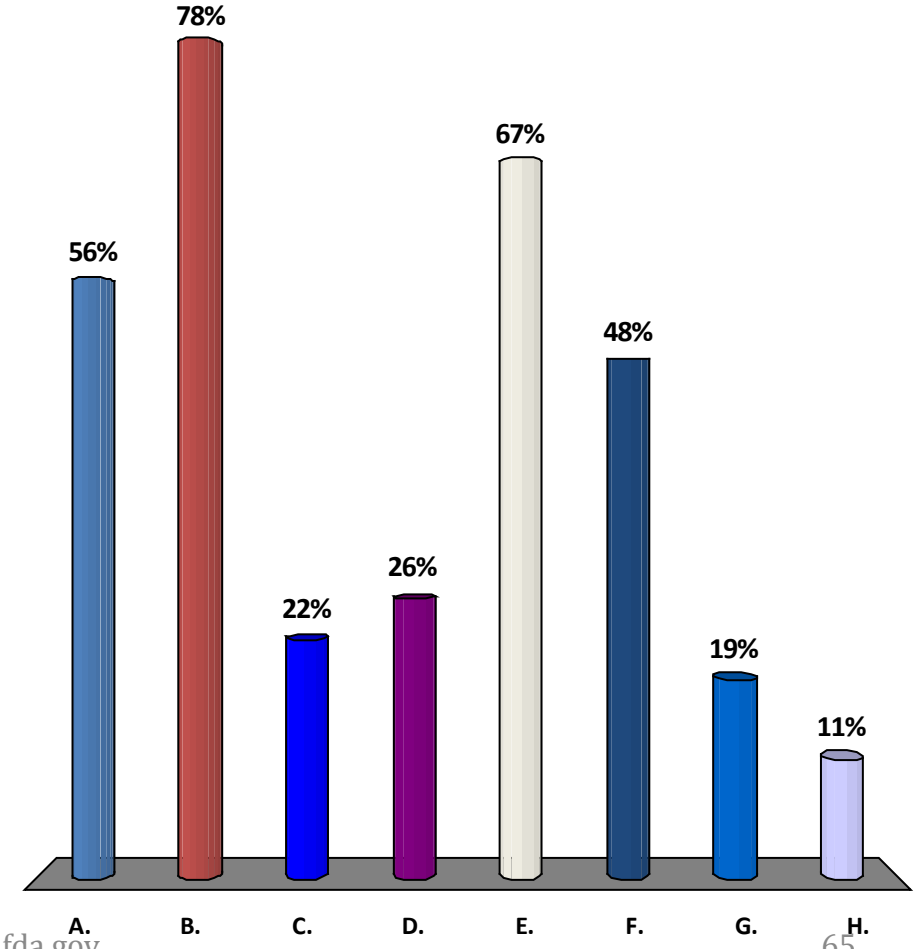
Have you ever used any of the following drug therapies to manage your organ transplantation? Check all that apply

A. Calcineurin Inhibitors (such as tacrolimus or cyclosporine)
B. Glucocorticoids (such as prednisone)
C. Purine antagonist (such as azathioprine or mycophenolate mofetil)
D. Mammalian target of rapamycin inhibitors (such as sirolimus, everolimus)
E. Antidepressant drugs (such as Elavil (amitriptyline), Prozac (duloxetine), Effexor (venlafaxine))
F. Opioid pain medicines
G. Other drug therapies not mentioned
H. I'm not taking any drug therapies



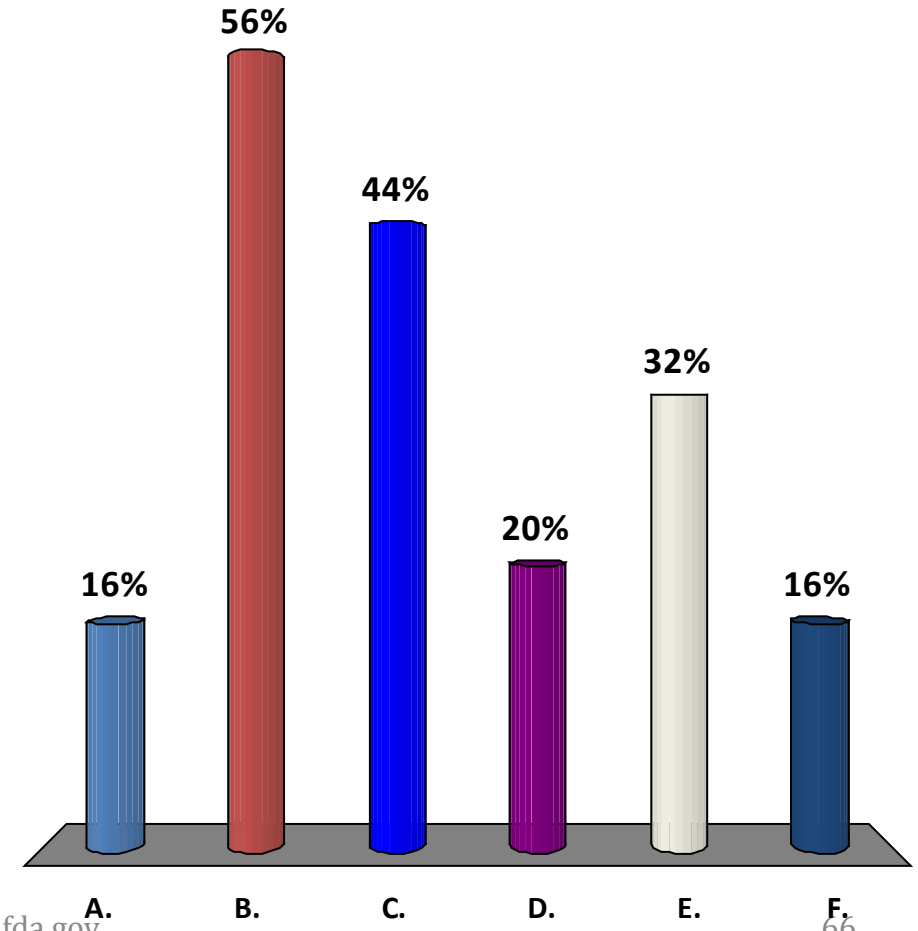
Besides the therapies mentioned previously, what else are you doing to manage any symptoms you have experienced because of your organ transplantation? Check all that apply.

A. Dietary and herbal supplements
B. Diet modifications and behavioral changes (such as limiting alcohol or tobacco use)
C. Complementary or alternative therapies (such as acupuncture or massage)
D. Physical or occupational therapy
E. Exercise and other physical activities
F. Over-the-counter products (such as ibuprofen or naproxen)
G. Other therapies not mentioned
H. I am not doing or taking any therapies to treat symptoms



In addition to preventing organ rejection, of the following factors, which two would you rank as most important to your decisions about using a therapy to manage your organ transplantation? Please choose two.

A. The frequency of administration of the drug (i.e twice a day or once a day)
B. The common side effects of the treatment (such as nausea, fatigue, and weight gain)
C. The possibility of rare, but serious side effects (such as nerve and liver damage)
D. The possibility of interactions with medications for other comorbidities (such as hypertension or diabetes)
E. Your access to this treatment (for example, insurance coverage)
F. Other considerations



LUNCH

U.S. FOOD & DRUG ADMINISTRATION

Afternoon Scientific Session: Medication Adherence and Experience with Intervention

Session #1: Causes of Late Allograft Loss and The Impact of Nonadherence, Definitions, Terms, and Background

Session #2: Interventions to Mitigate Non-Adherence

U.S. FOOD & DRUG ADMINISTRATION

Opening Remarks

Ozlem Belen, MD, MPH
Deputy Director for Safety,
Division of Transplant and Ophthalmology Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

Afternoon Scientific Session: Medication Adherence and Experience with Intervention

- Session #1: Causes of Late Allograft Loss and The Impact of Nonadherence, Definitions, Terms, and Background

- Session #2: Interventions to Mitigate Non-Adherence

Scientific Discussion 1: “Causes of late allograft loss and the impact of nonadherence, definitions, terms and background”

Overview of Late Allograft Outcomes

Etiology, Risk Factors and Natural History

FDA Workshop, Washington DC
27 Sept 2016

Peter Nickerson, MD, FRCPC, FCAHS
Flynn Family Chair in Renal Transplantation
Professor of Internal Medicine and Immunology

University of Manitoba

Health Sciences Centre Winnipeg

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Relevant Financial Relationship Disclosure Statement

Peter Nickerson, University of Manitoba, Winnipeg, Canada

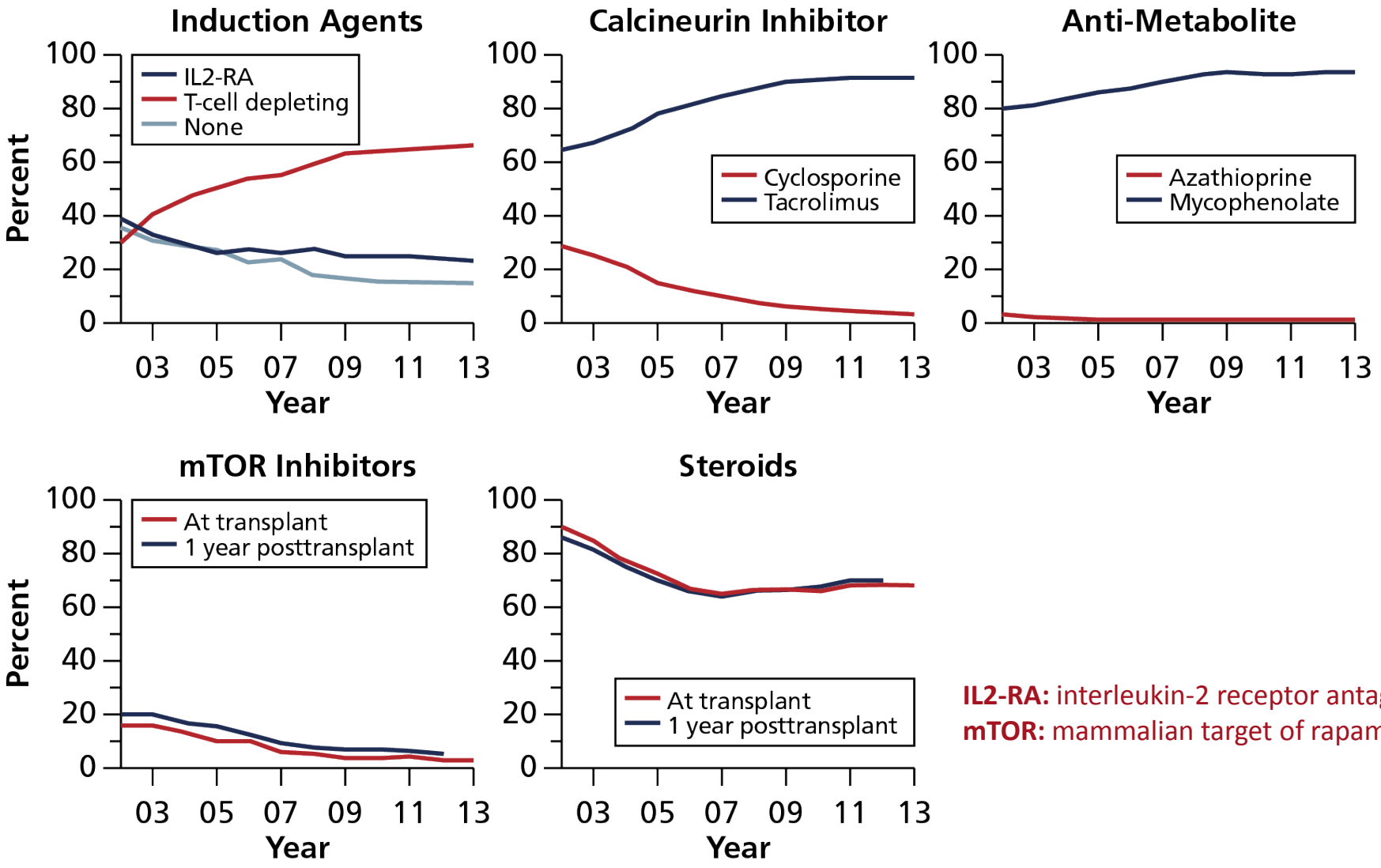
Consultant for Novartis and Astellas

AND

My presentation does not includ discussion of off-label
or investigational use of drugs

2005 to 2015 Focus

T-cell depletion to minimize CNI / Steroid utilization

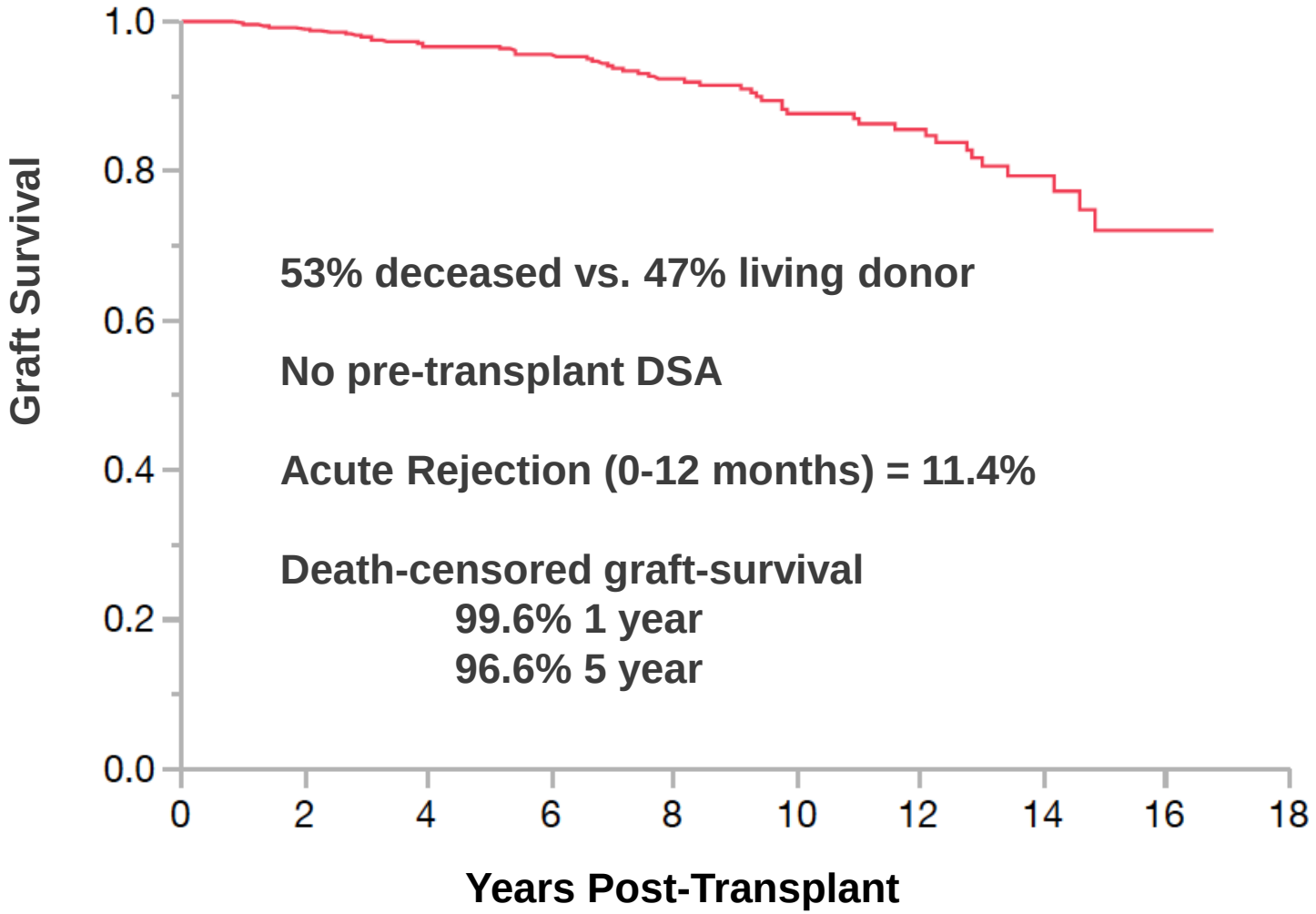


IL2-RA: interleukin-2 receptor antagonist
mTOR: mammalian target of rapamycin

Matas et al., AJT (2015) 15 (suppl 2):1-34

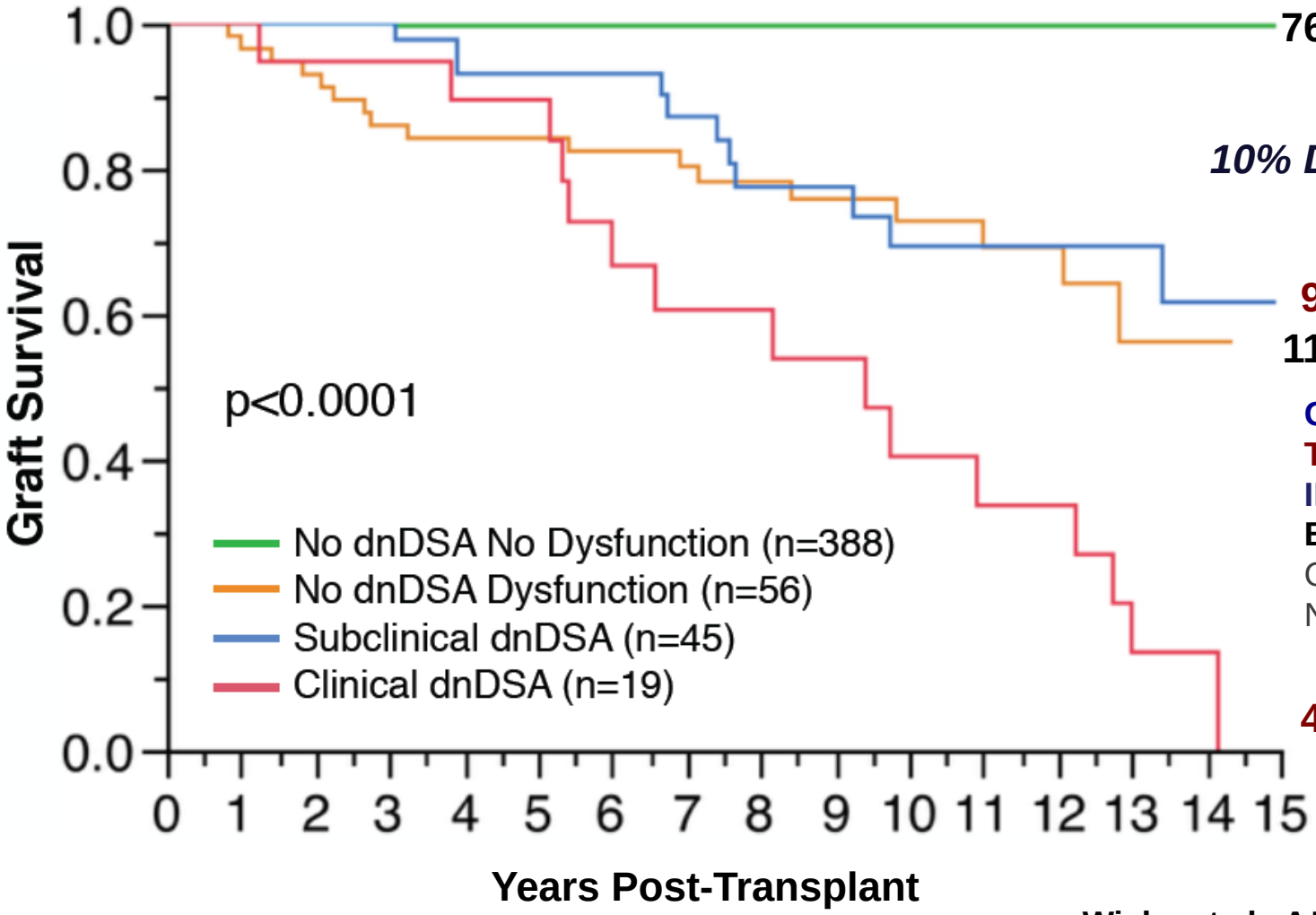
Short-Term Outcome Excellent

Consecutive Adult and Pediatric Kidney Transplants (n=508, 1999 to 2012)



Etiology of Late Allograft Dysfunction and Loss

Consecutive Adult and Pediatric Kidney Transplants (n=508, 1999 to 2012)



76% Stable Function

9% (n=46)

10% Death with Function

1% (n= 5)

9% Subclinical DSA

11% Other Causes

GN+IFTA (n=20) 4%
TCMR+IFTA (n=10) 2%
IFTA (n= 8) 1.6%
BK Nephro(n= 2) 0.4%
Other (n= 6)
Not Bx (n=10)

4% Clinical DSA

Wiebe et al., AJT (2015) 15: 2921-2930

De novo DSA and ABMR

INCIDENCE

Reported incidence of *de novo* DSA varies significantly

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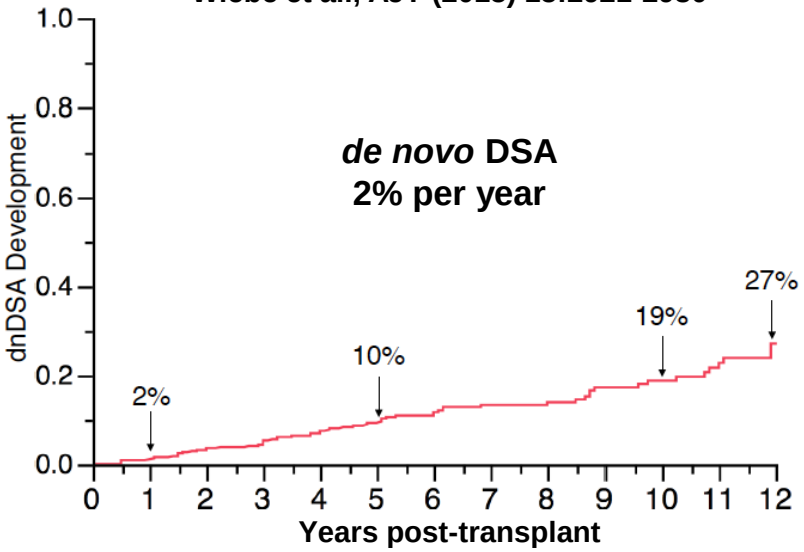
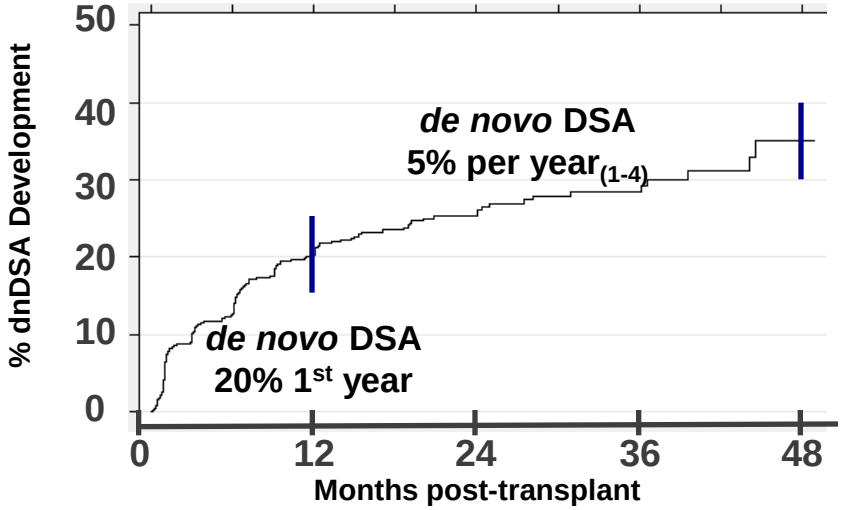
Wiebe et al., AJT (2015) 15:2921-2930

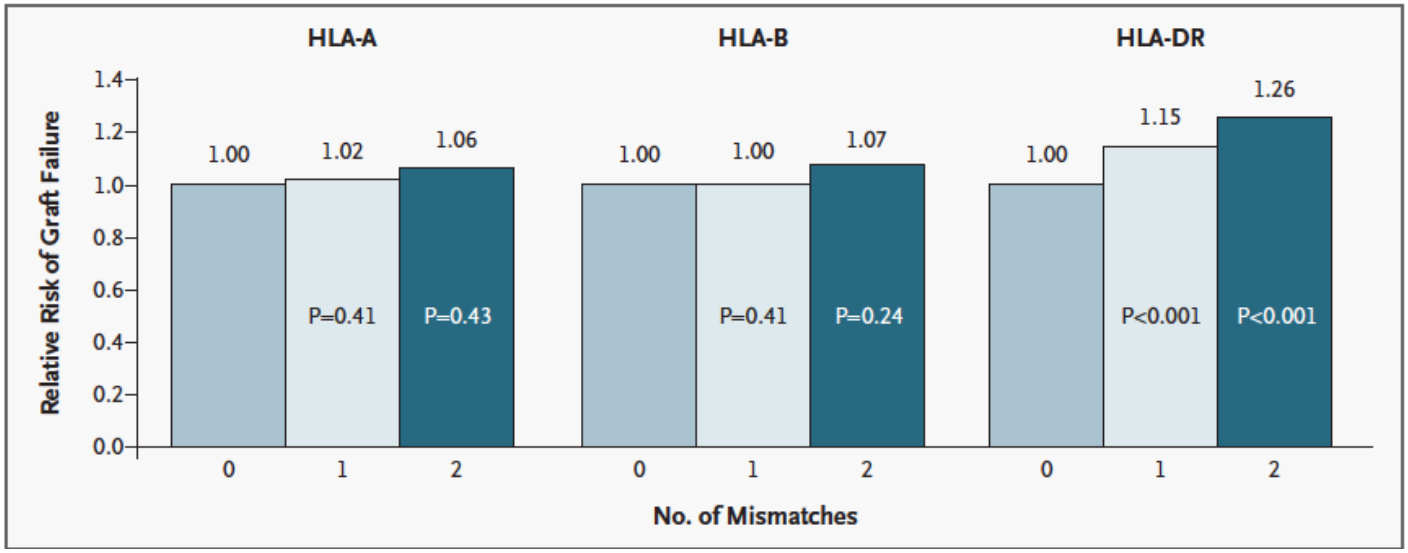


DeVos et al., Transplantation (2014) 97:534-540



Ref.	1st Tx	Defn to Rule out Pre-Tx DSA	"*de novo*" DSA			Induction (Depletional)		Race			
			1st Mo	1st Yr	>1st Yr	Thymo	Campath	Cauc	AA	Hisp	Asian
Cooper	**n.a.**	**FCXM**	**15.6%**	**27.0%**	0% yr 2	**66%**	0%	69%	7%	17%	n.a.
DeVos	**93%**	**>2000 MFI**	**8.0%**	**20.0%**	**5.0%/yr**	**61%**	0%	42%	**27%**	24%	n.a.
Heilman	**91%**	**>1000 MFI**	**8.2%**	**17.6%**	n.a.	26%	**61%**	n.a.	5%	n.a.	n.a.
Everly	**100%**	**>1000 MFI**	**3.0%**	**11.0%**	**2.3%/yr**	13%	0%	n.a.	**64%**	n.a.	n.a.
Wiebe	**95%**	**>500 MFI**	**0.0%**	**2.0%**	**2.0%/yr**	9%	0%	69%	2%	0%	11%

Roberts et al., N Engl J Med (2004) 350:545-51



Risk Factors for *de novo* DSA and ABMR

HLA Mismatch

RENAL HOMOTRANSPLANTATION IN IDENTICAL TWINS*

Joseph E. Murray, John P. Merrill and J. Hartwell Harrison

Surg. Forum VI: 432–436, 1955

HLA Class II MM correlates with *de novo* DSA

University of Manitoba

STUDY	Dominant de novo DSA			HLA Mismatch	
	I	II	I+II	DR MM	DQ MM
Worthington et al.	X				
Hourmant et al.		**X**		**X**	
Piazza et al.		**X**			
Lachmann et al.		**X**			
Scornik et al.		**X**			
Lachmann et al.		**X**			
Hidalgo et al.		**X**			
Yabu et al.			X		
Fotheringham et al.	X				
Cooper et al.		**X**		**HLA Mismatch**	
Liefeldt et al.		**X**		**HLA Mismatch**	
Willicombe et al.		**X**		**X**	**X**
Ginevri et al.		**X**			
De Kort et al.		**X**			
Everly et al.		**X**			**X**
Wiebe et al.		**X**		**X**	**X**
De Vos et al.		**X**		**HLA Mismatch**	

Wiebe et al., Current Opinion Organ Transplant (2013) 18:470

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Risk Factors for *de novo* DSA and ABMR

TCMR / IMMUNOSUPPRESSION

TCMR correlates with subsequent *de novo* DSA / ABMR

Early clinical TCMR (<1yr) linked to development of *de novo* DSA / ABMR

Hourmant et al., JASN (2005) 16:2804-2812
Wiebe et al., AJT (2012) 12:1157-1167
Liefeldt et al., AJT (2012) 12:1192-1198
El Ters et al., AJT (2013) 13:2334-2341
Chemouny et al., Transplantation (2015) 99:965-972
Yamamoto et al., Transplantation (2015) ePub

Early Subclinical tubulointerstitial inflammation

Linked to → ***de novo* DSA**

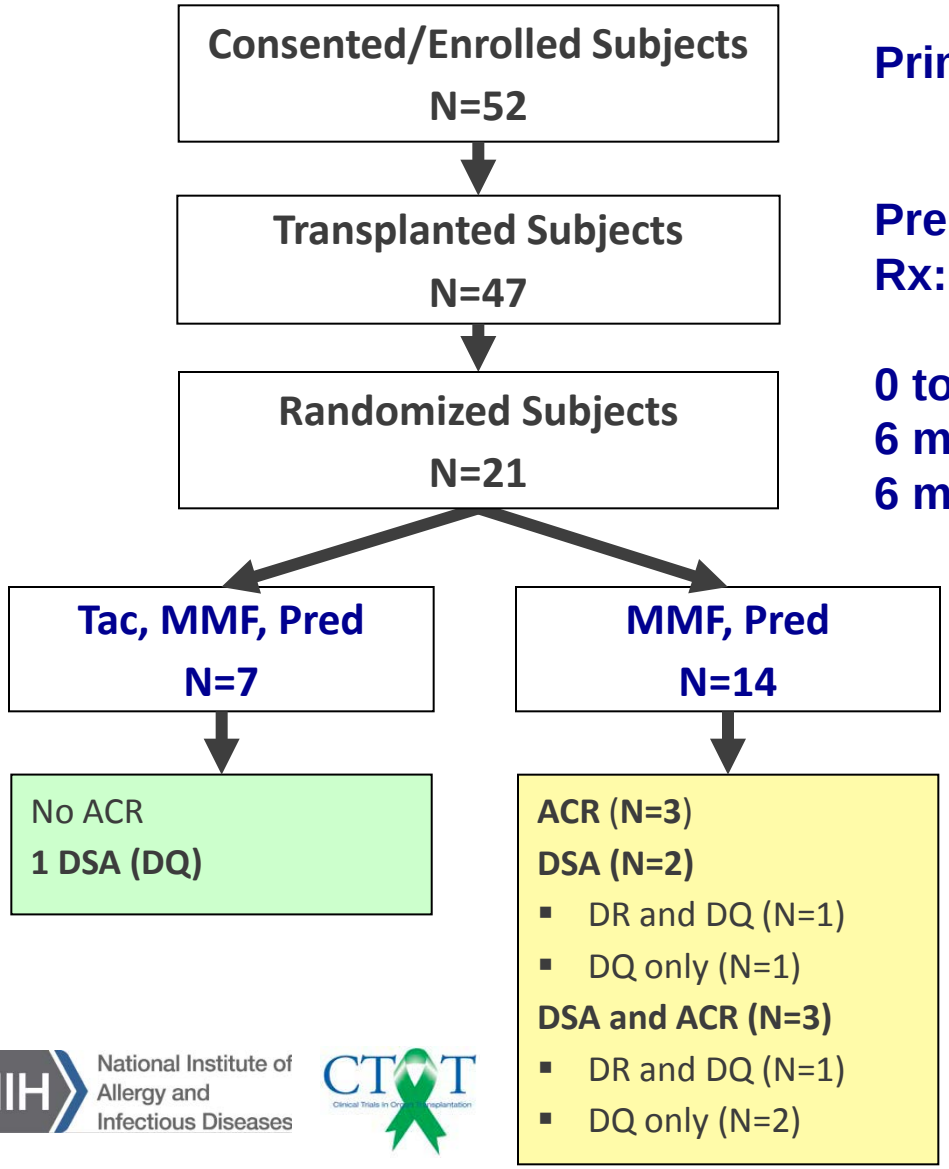
Wiebe et al., AJT (2012) 12:1157-1167
El Ters et al., AJT (2013) 13:2334-2341

Linked to → **Chronic Antibody-Mediated Rejection**

(TG, PTC BM multi-layering; C4d+; DSA)

Moreso et al., Transplantation (2012) 93:41-46

Tacrolimus withdrawal in *Immune Quiescent* Kidney Transplant Recipients (CTOT-09)



Primary Living Donor Transplants

Pre Transplant HLA Ab: No DSA, PRA <30%
Rx: Thymo, Tacrolimus, MMF, Prednisone

0 to 6 mo course: No Acute Rejection
6 mo Protocol Biopsy: Normal Histology
6 mo Antibody Screen: No DSA

Tacrolimus tapered over 3 months

DSMB halted trial
- **Predetermined stopping rules**

Quiescence ≠ Low Risk to Minimize

Hricik et al., JASN (2015) 26:3114-22

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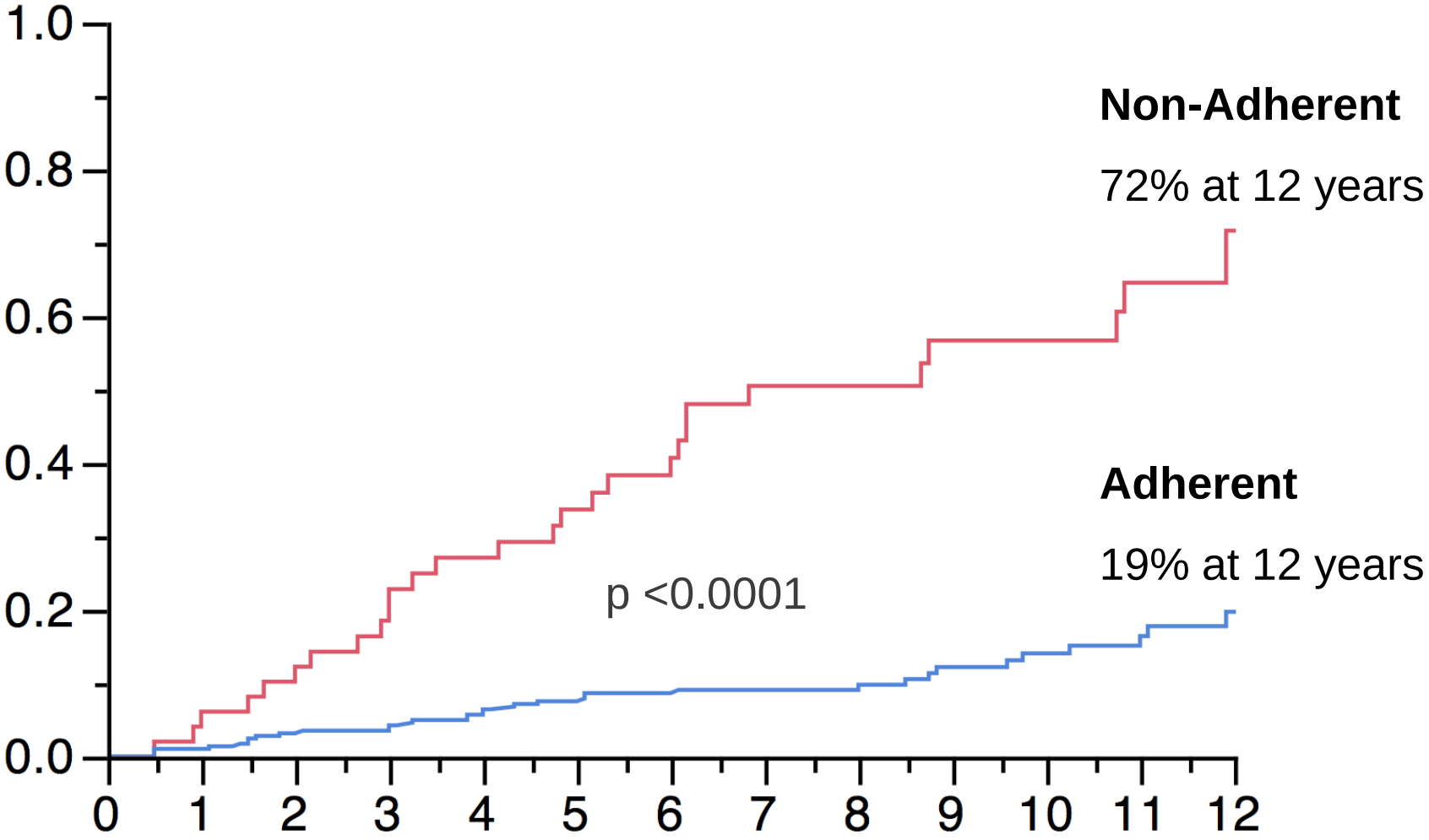
Risk Factors for *de novo* DSA and ABMR

NON-ADHERENCE

Non-Adherence is a major risk factor for *de novo* DSA



Wiebe et al., AJT (2015) 15: 2921-2930

Predictive Patterns of Early Medication Adherence in Renal Transplantation

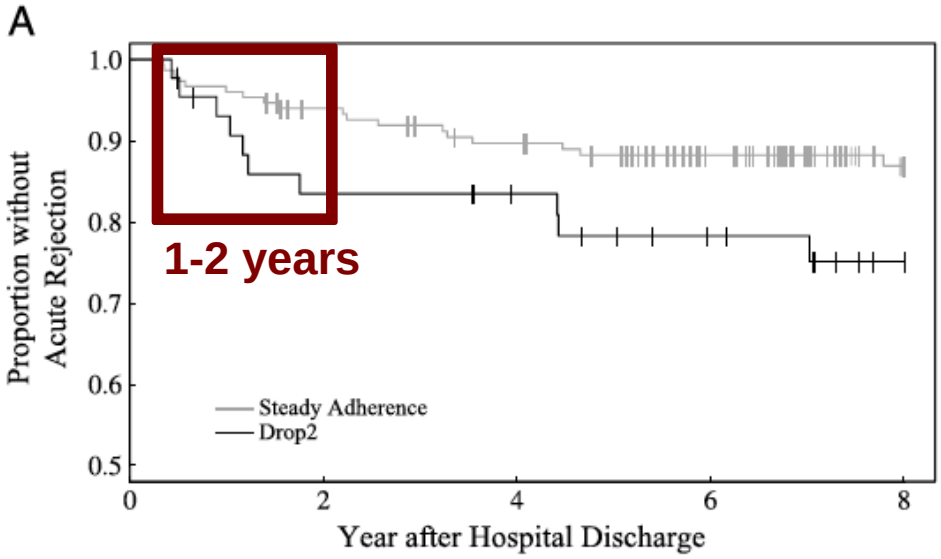
Thomas E. Nevins,[1,4] William N. Robiner,[2] and William Thomas[3]

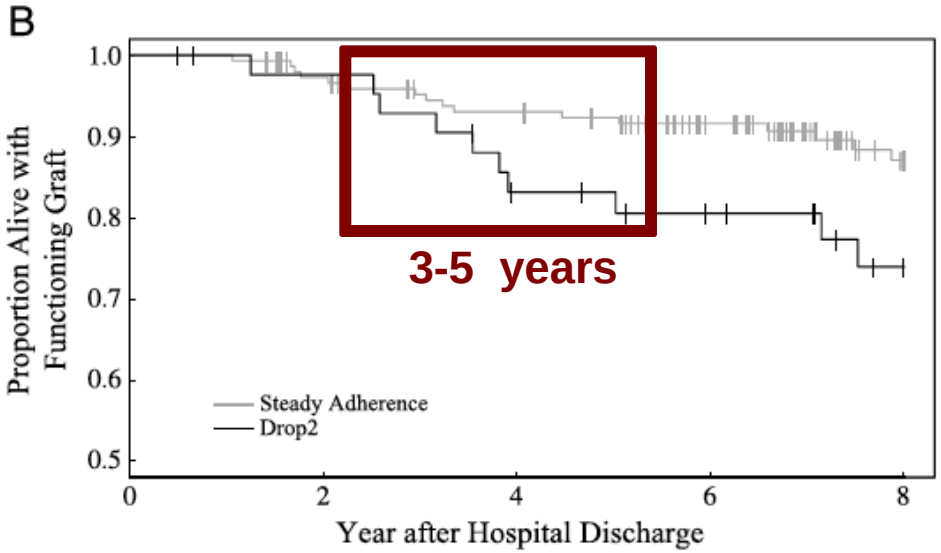
MEMS
(Medication Event Monitoring System)

195 patients

- **44 (22.6%)** decreased adherence by 7% or more in **month 2** post tx

  → **Late Acute Rejection**
  → **Early Graft Loss**





Transplantation (2014) 98:878-884

Nominal Logistic Regression for *dn*DSA Predictors

***de novo* DR DSA**	**p value**	**OR**
Non-Adherence	0.002	5.30
DR$\beta_{1/3/4/5}$ MM	0.002	2.14†
TCMR preceding dnDSA	0.002	2.38†

† per unit change

***de novo* DQ DSA**	**p value**	**OR**
Non-Adherence	<0.0001	9.53
DQ$\alpha\beta$ MM	0.01	1.62†
Recipient Age	0.03	0.97†

Wiebe et al AJT 2012; 12: 1157-1167

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De novo DSA and ABMR

HISTOLOGIC CORRELATES WITH OUTCOME

At onset of *de novo* DSA, 76% meet ABMR criteria (Banff 2013)

Banff Grade	0	1	2	3
g	(55%,	32%,	13%,	0%)
i	(28%,	24%,	24%,	24%)
t	(39%,	32%,	11%,	18%)
v	(94%,	3%,	0%,	3%)
ptc	(24%,	10%,	45%,	21%)
C4d	(52% C4d positive)			
cg	(87%,	8%,	5%,	0%)
ci	(29%,	37%,	19%,	5%)
ct	(11%,	53%,	26%,	10%)
cv	(40%,	47%,	13%,	0%)

TCMR (Banff 2007) common (91% with ABMR)

- 32% Borderline
- 29% ≥ Grade 1

Only 18% have no TCMR or ABMR

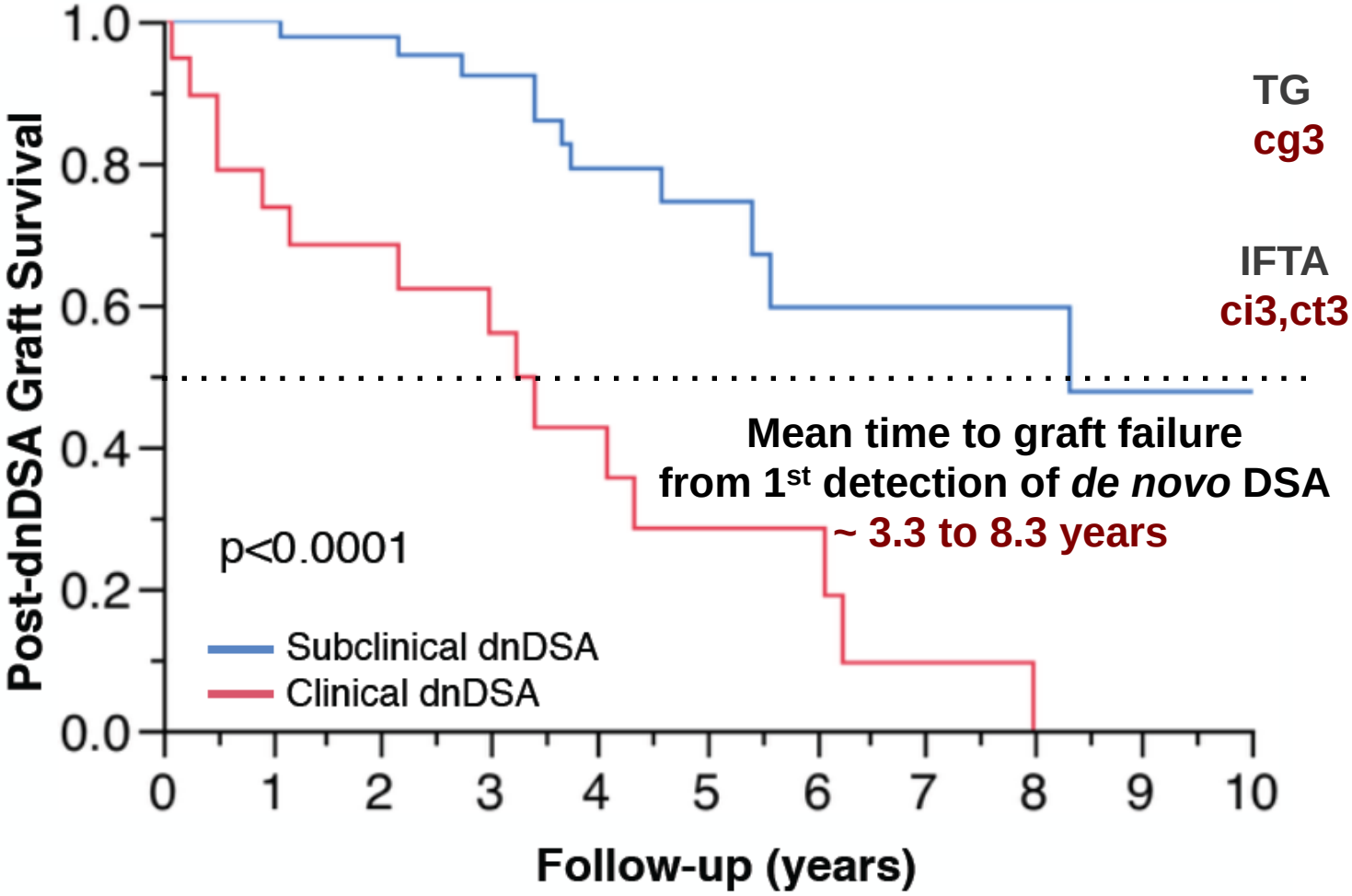
Transplant glomerulopathy uncommon

IFTA common

Wiebe et al., AJT (2015) 15: 2921-2930

Time to Graft Loss from *de novo* DSA Onset

Consecutive Adult and Pediatric Kidney Transplants (n=508, 1999 to 2012)



Wiebe et al., AJT (2015) 15: 2921-2930

Independent Correlates of Banff Chronic Scores

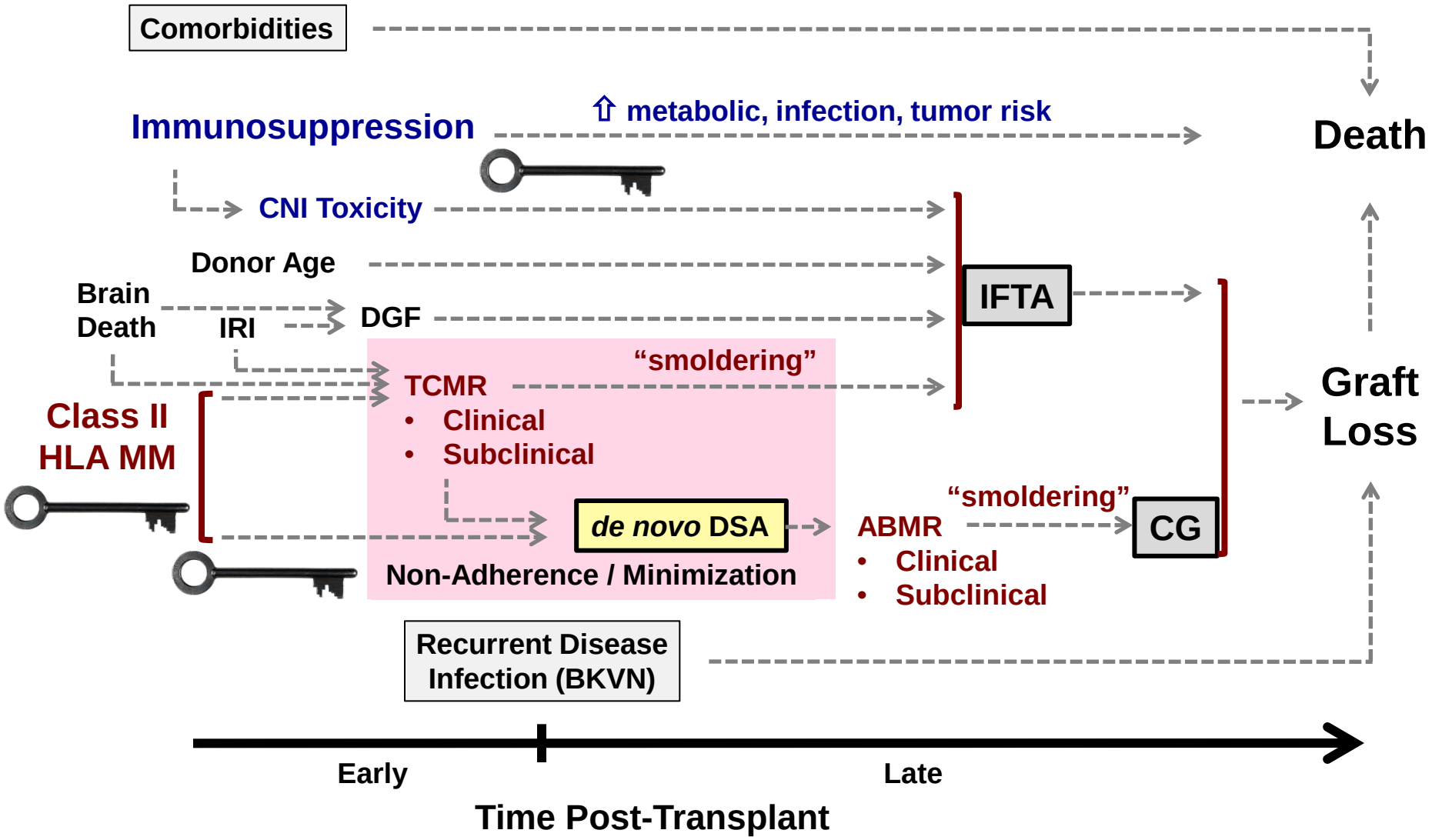
University of Manitoba

Multivariate Analysis

Banff Score	n (% with score)	Cellular Rejection ≤ 12 months OR per rejection (95%CI)	*dn*DSA Development OR of yes vs. no (95%CI)	Time Post-Transplant OR per year (95%CI)	Non-Adherence OR of yes vs. no (95%CI)
cg≥1	89 (8%)	1.16 (0.8-1.6)	4.42 (2.5-8.1)***	1.32 (1.2-1.4)***	1.64 (0.9-2.9)
cg≥2	30 (3%)	0.70 (0.3-1.3)	10.36 (3.6-37.8)***	1.37 (1.3-1.5)***	1.24 (0.5-2.9)
cg=3	13 (1%)	0.82 (0.3-2.1)	18.50 (3.2-350.9)***	1.44 (1.3-1.7)***	0.90 (0.2-3.3)
ci≥1	558 (51%)	1.55 (1.3-1.9)***	1.00 (0.7-1.4)	1.40 (1.2-1.5)***	1.40 (1.3-1.5)**
ci≥2	177 (16%)	1.73 (1.4-2.1)***	1.28 (0.8-1.9)	1.27 (1.2-1.3)***	2.04 (1.3-3.1)***
ci=3	39 (4%)	1.30 (0.9-1.9)	0.63 (0.3-1.4)	1.30 (1.2-1.4)***	3.36 (1.5-7.6)**
ct≥1	671 (62%)	1.30 (1.1-1.6)**	0.70 (0.5-1.0)	1.83 (1.6-2.1)***	1.52 (1.0-2.2)*
ct≥2	168 (15%)	1.58 (1.3-2.0)***	1.10 (0.7-1.7)	1.32 (1.2-1.4)***	2.28 (1.4-3.6)***
ct=3	53 (5%)	1.31 (0.9-1.8)	0.99 (0.5-2.0)	1.29 (1.2-1.4)***	4.19 (2.1-8.6)***
cv≥1	392 (38%)	1.26 (1.1-1.5)**	0.86 (0.6-1.2)	1.24 (1.2-1.3)***	1.50 (1.1-2.2)*
cv≥2	88 (8%)	1.40 (1.1-1.8)**	1.15 (0.7-2.0)	1.16 (1.1-1.2)***	1.16 (0.6-2.1)
cv=3	13 (1%)	1.19 (0.5-2.2)	1.07 (0.3-4.5)	1.21 (1.0-1.4)*	3.81 (0.9-15.9)

Wiebe et al., AJT (2015) 15: 2921-2930

Causal Pathways linked to Kidney Allograft Loss



Wiebe et al., Transplantation (ePub)

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Robert Fairchild
Richard Formica
Emilio Poggio
Nancy Bridges
David Ilke

Aspects of Non-Adherence

Definitions-Identification/Detection-Risk Factors

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Director, Transplant Clinical Research
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Disclosures

I have financial relationships within the last 12 months with:

Clinical Research Grants

- Novartis, Astellas, Veloxis, Onyx, GSK, Prolong, Bristol-Myers Squibb, Chimerix, Sanofi, and FDA

Advisory Board

- Genzyme-Sanofi

Speakers Bureau

- Sanofi, Veloxis

This presentation does not include discussion of off-label or investigational use of any drugs

Objectives

- Differentiate medication non-adherence and compliance
- Identify risk factors for non-adherence in solid organ transplant recipients
- Describe measures to quantitate medication non-adherence

Non-Adherence

- Age Old Problem
  - "Keep watch also on the fault of patients which makes them lie about taking of things prescribed."
    - Hippocrates, circa 500 B.C.
  - "Drugs don't work if people don't take them."
    - C. Everett Koop, 1985
- Transplantation can no longer accept the status quo
  - "The first shot is our best shot" for transplant success
  - Despite millions in investment, a "magic" drug or procedure to render adherence irrelevant is not on the horizon
  - Are federal mandates necessary to properly resource adherence initiatives if adherence continues to be neglected?

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Medication Adherence vs. Compliance

- Medication Adherence
  - The extent to which patients take medications as prescribed by health care providers.

- Compliance
  - Passive act of the patient to follow the providers orders

Osterberg, L., & Blaschke, T. (2005). Adherence to medication. *New England journal of medicine*, *353*(5), 487-97.

Medication Adherence

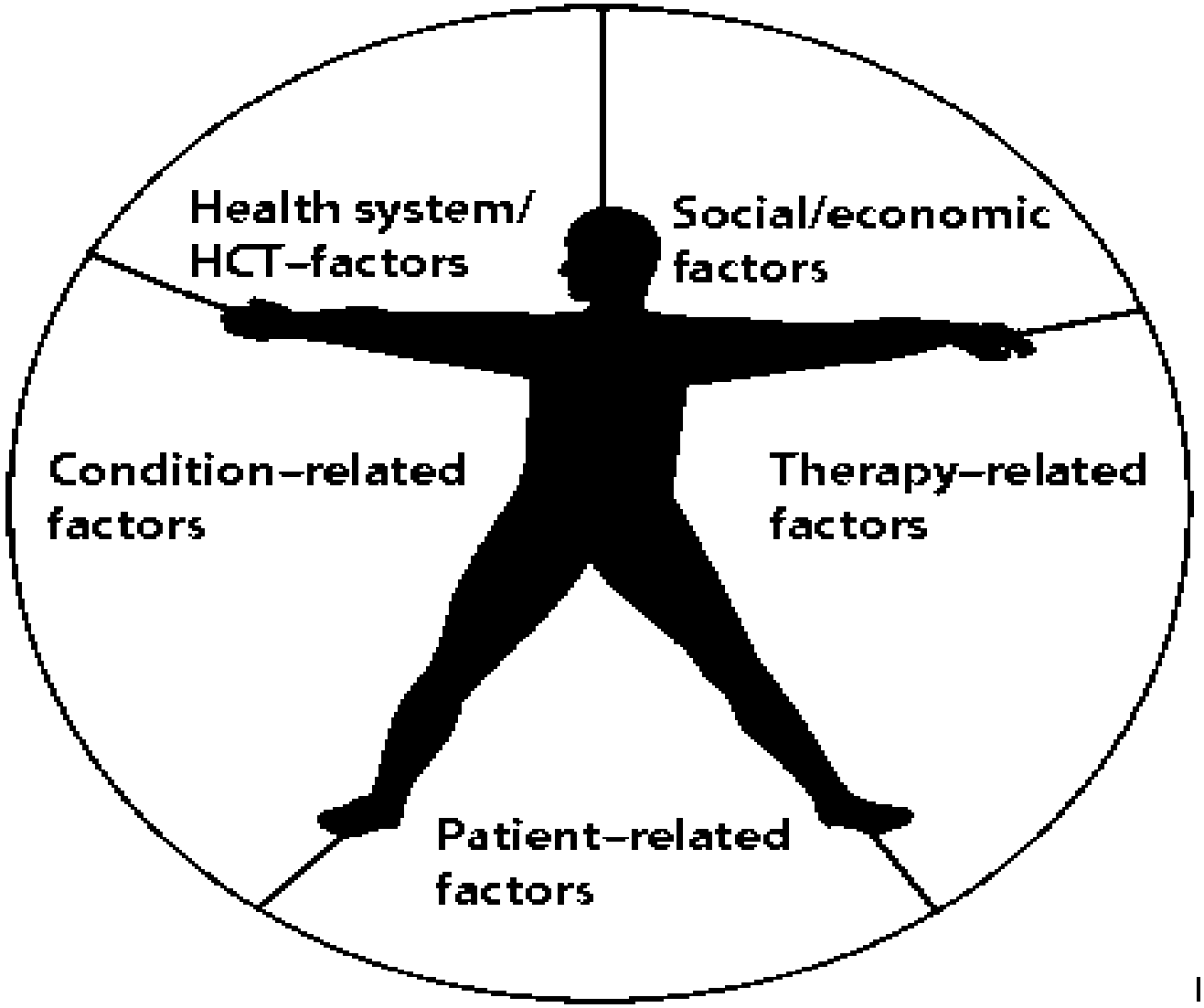
- A behavioral process that is influenced by many factors
- Assumes the patient has the knowledge, motivation, skills and resources to follow the health care providers prescription

Medication Non-Adherence

- Intentional medication non-adherence
  - "Active process whereby the patient chooses to deviate from the treatment regimen."
- Unintentional medication non-adherence
  - "Passive process in which the patient may be careless or forgetful about adhering to treatment regimen."

Ho, P., Bryson, C., , & Rumsfeld, J. (2009). Medication adherence: Its importance in Cardiovascular Outcomes. *Circulation*, *119*(23), 3031.

Five Dimensions of Adherence



Transplantation 2007:83:858-873
American College of Preventative Medicine

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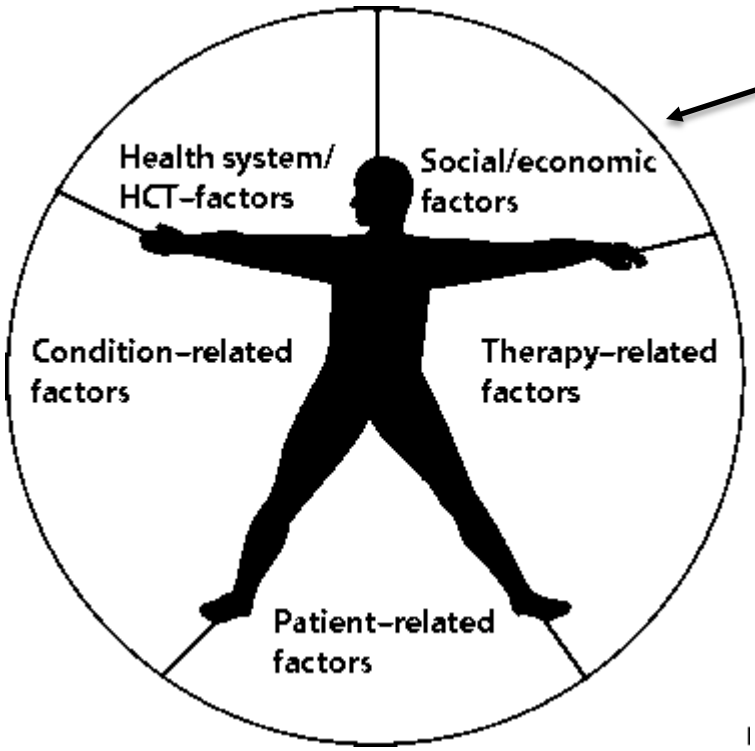
Transplant Specific Social/Economic Factors



Younger Patient
Male Gender
Non Caucasian
Non US resident
Poor social support
Poor transportation
Literacy

Transplantation 2007:83:858-873
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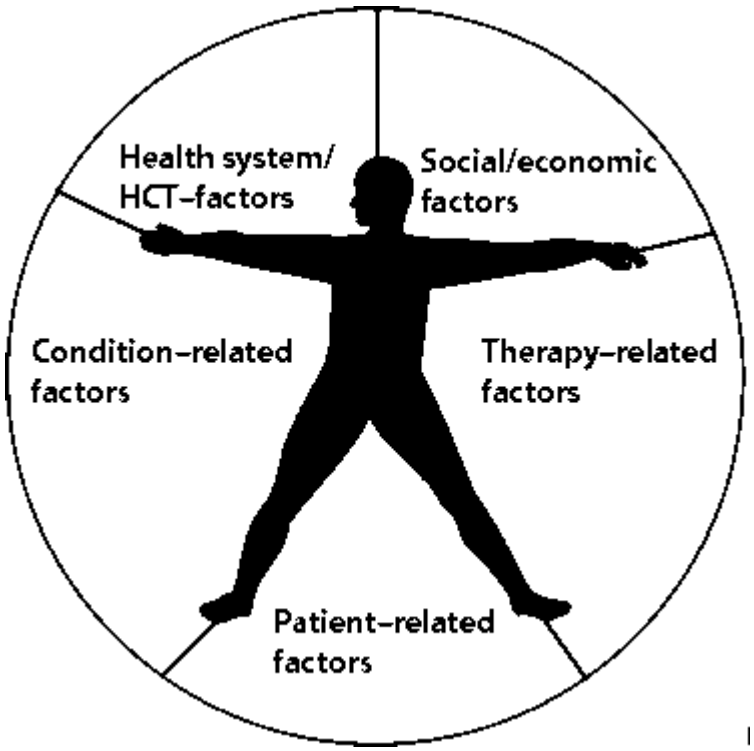
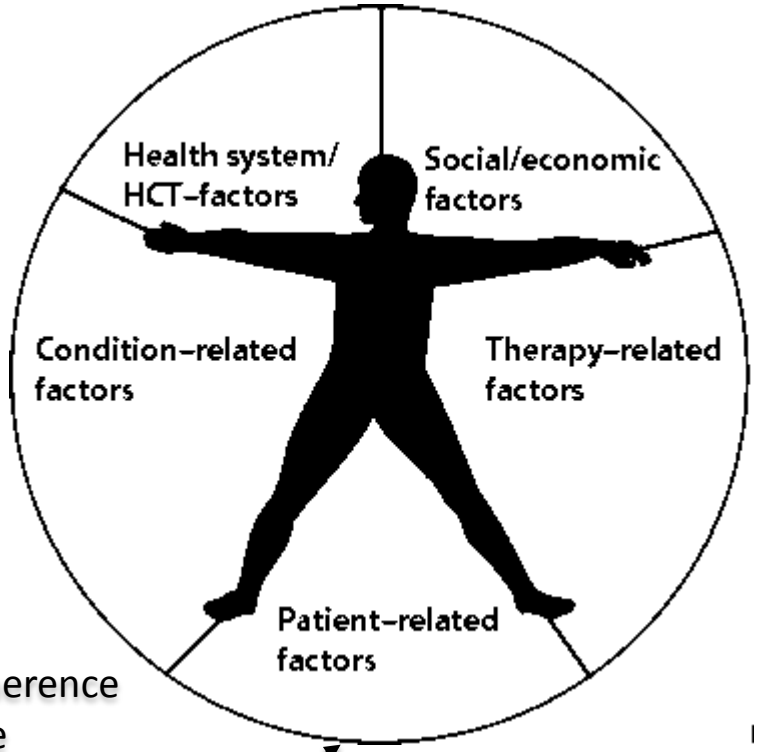
Transplant Specific Therapy-Related Factors



Complex Medical Regimens
Higher Medication Toxicity
Lack of medication education
No pillbox/reminder system

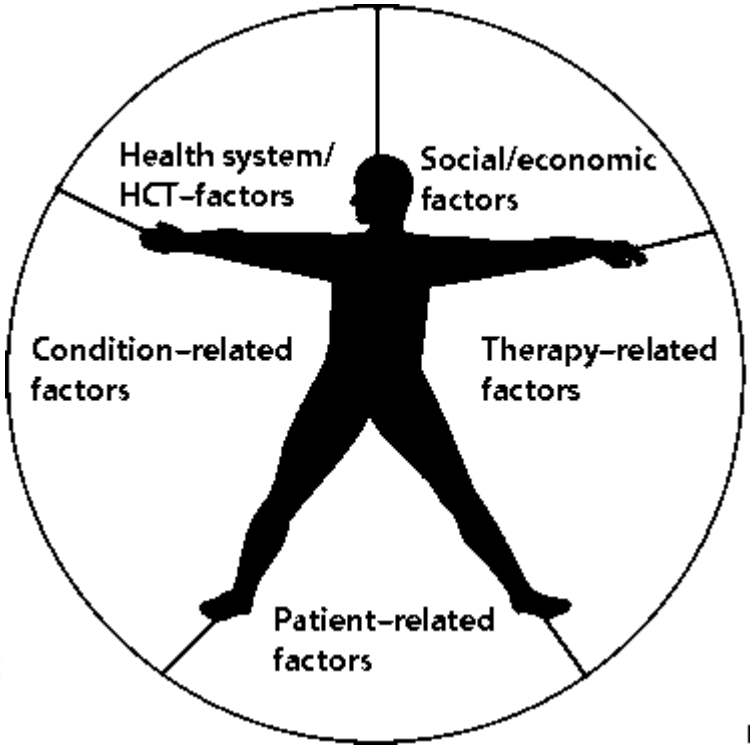
Transplantation 2007:83:858-873
American College of Preventative Medicine

Transplant Specific Patient-Related Factors



History of non-adherence
Adolescence
Psychologic disorder (depression)
Cognitive impairment
Substance abuse
Negative beliefs in medication

Transplant Specific Condition-Related Factors



High Symptom Distress
Development of NODAT
Increased time post transplant

Transplantation 2007:83:858-873
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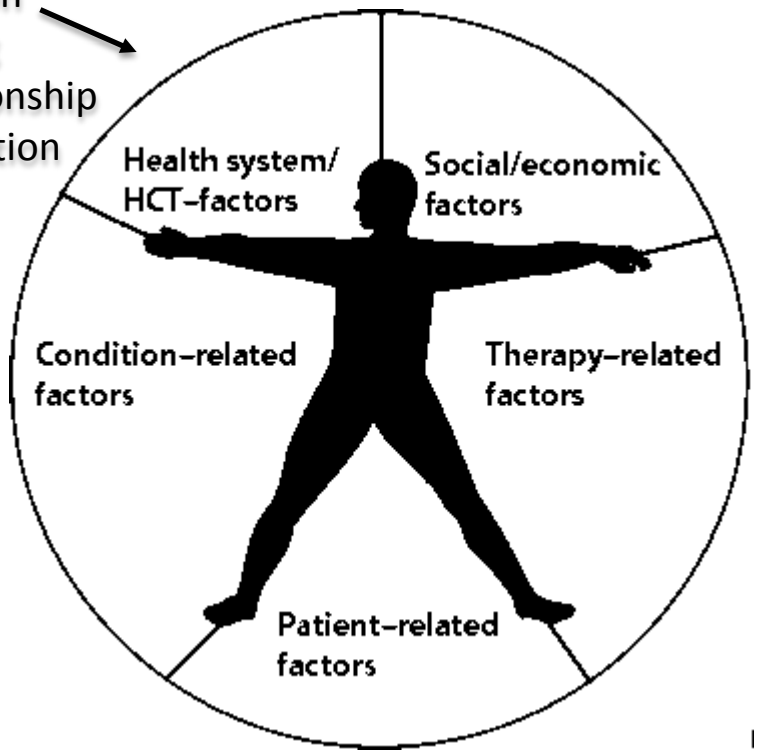
Transplant Specific Health System/Care Factors

Medication costs
Poor access to medication
Poor aftercare planning
Poor physician-patient relationship
Poor physician communication



Five Dimensions of Adherence

Transplantation 2007:83:858-873
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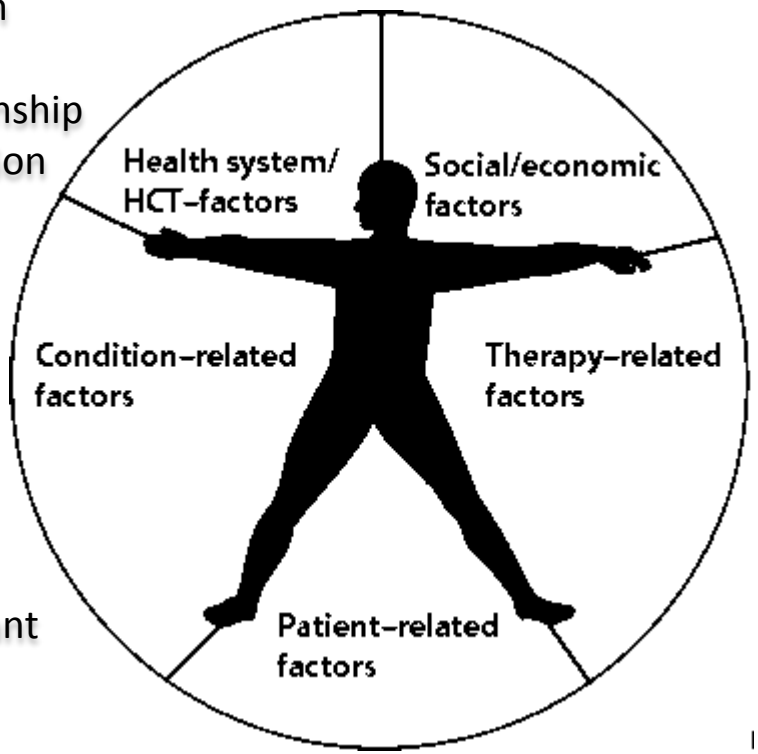
Which Factors are MODIFIABLE??

Medication costs
Poor access to medication
Poor aftercare planning
Poor physician-patient relationship
Poor physician communication



Younger Patient
Male Gender
Non Caucasian
Non US resident
Poor social support
Poor transportation
Literacy

High Symptom Distress
Development of NODAT
Increased time post transplant

Complex Medical Regimens
Higher Medication Toxicity
Lack of medication education
No pillbox/reminder system

History of non-adherence
Adolescence
Psychologic disorder (depression)
Cognitive impairment
Substance abuse
Negative beliefs in medication

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Pharmacoadherence Measures

- Objective measures
  - Direct measures
    - Provide evidence that medication has been consumed or taken (example: Direct observation, ie Belatacept)
  - Indirect measures
    - Provide evidence suggesting that medication has been consumed or taken (example: Pill counts, tacrolimus drug levels, pharmacy refill records, medication possession ratio)
- Subjective measures
  - Provide testimony that medication has or has not been taken (example: Self report, assessment by others)

Direct Observation Options in Transplantation

- Advantages
  - Objective
  - Highly specific
  - Not invasive
- Disadvantages
  - Feasibility issues
  - Labor intensive (e.g., training observers)
  - Not practical
  - Expensive
  - Not an option for all transplant recipients

Bennet Johnson S. *Diabetes Care* 1992;15:1658-67; Farmer KC. *Clin Ther* 1999;21:1074-90; Hill J. *Musculoskeletal Care* 2005;3:143-56; Partridge AH, et al. *J Natl Cancer Inst* 2002;94:652-61.

Drug Concentration Monitoring

- Advantages
  - Objective
  - May be part of standard care
  - Direct assessment of whether patient has taken medication

- Disadvantages
  - Snapshot of behavior
  - Affected by factors other than pharmacoadherence (e.g., metabolism, drug-drug/drug-food interactions, poor absorption)
  - Cost
  - Invasive

Butler et al. *Transplantation* 2004;77:786-89; Chisholm MA, et al. *Transplantation* 2001;70:1240-44; Chisholm MA, et al. *Clin Transplant* 2001;15:330-36; Chisholm MA, et al. *Nephrol Dial Transplant* 2005;20:181-88; Chisholm MA, et al. *Clin Transplant* 2005;19:77-82; Chisholm MA, et al. *Am J Health-Syst Pharm* 2005;68:1775-81; Chisholm MA, et al. *Patient Educ Couns* 2005;59:13-20.

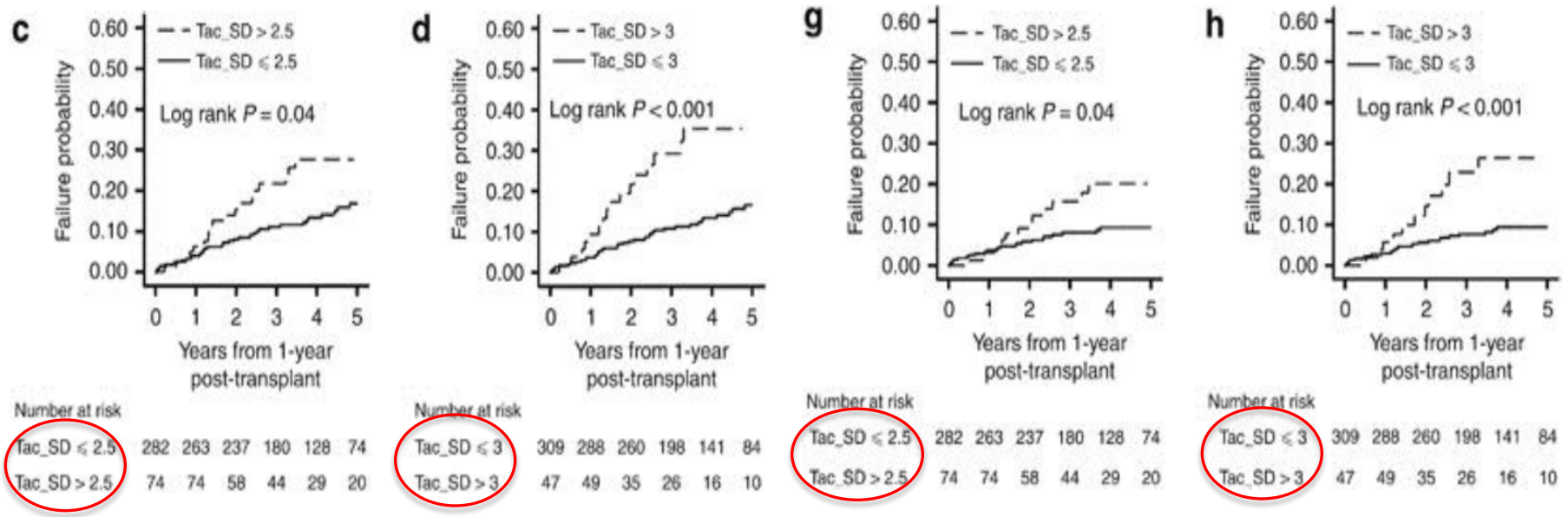
Tacrolimus Variability: Impact on Late Outcomes

Composite endpoint

Late acute rejection(>1yr), or TG and total GL

Composite endpoint

Late acute rejection(>1yr), or TG and total GL (excluding death with function)



- Tacrolimus variability assessed only during stable doses >1year post txp
- Tac SD thresholds tested included breaks at 1.5, 2, 2.5, and 3. HR ↑ 27% for a each 1 unit Tac SD, respectively
- No significant changes when adjusted for age, sex, eGFR or AR at 1 year

Kidney Int 2014;85:1404-1411

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Electronic Monitoring

- Advantages
  - Objective
  - Indicate time/date of bottle or pill box opening (real-time tracking; detects poor pharmacoadherence to dosing schedule)
  - Detects pill dumping when used in correlation with pill counts
  - Not invasive
- Disadvantages
  - Cost
  - Not effective with liquid medications
  - Can malfunction, lose data
  - Device may be bulky/inconvenient
  - May cause distress to patient (being monitored)
  - **Assumes medication removed from bottle/box is taken**

Blowey DL, et al. *Pediatr Nephrol* 1997;11:547-51; Butler et al. *Transplantation* 2004;77:786-89; DeGeest S, et al. *Clin Transplant* 2006;20:359-68; DeGeest S, et al. *J Cardiovasc Nurs* 2001;16:1-14; Feldman HI, et al. *Pharmacoepidemiol Drug Saf* 1999;8:1-14; Hardstaff R, et al. *Transplant Proc* 2003;35:796-97; Russell CL, et al. *Clin Nurs Res* 2007;16:153-63; Russell CL, et al. *Res Nurs Health* 2006;29:521-32.

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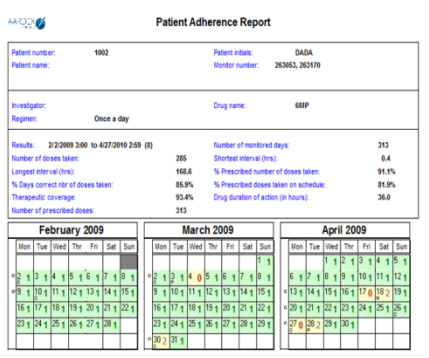
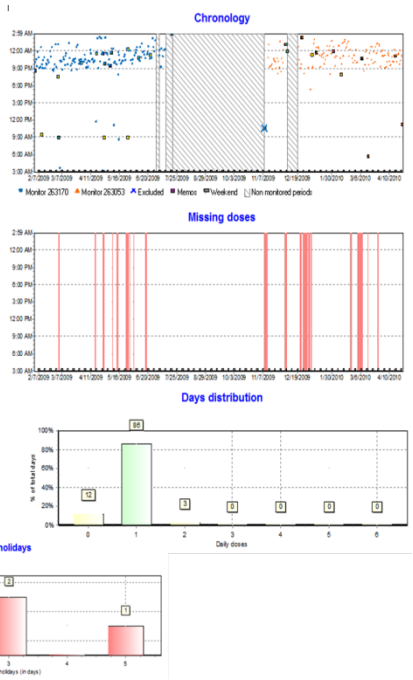
Strategies to Impact Non-Adherence

- Electronic Medication Monitors (MEMS) monitor revealed early medication adherence predicts adherence later
  - Tested with MMF, sirolimus and azathioprine in 195 kidney transplant recipients
  - Adherence between month 1-2 predicted adherence for 6mo and 12mo
  - Non-adherent patients more frequent, earlier AR and death censored graft loss
  - During month 1-3 – Adherence QID 84%, BID 91%, and QD 94%





Transplantation 2014;98:878-884

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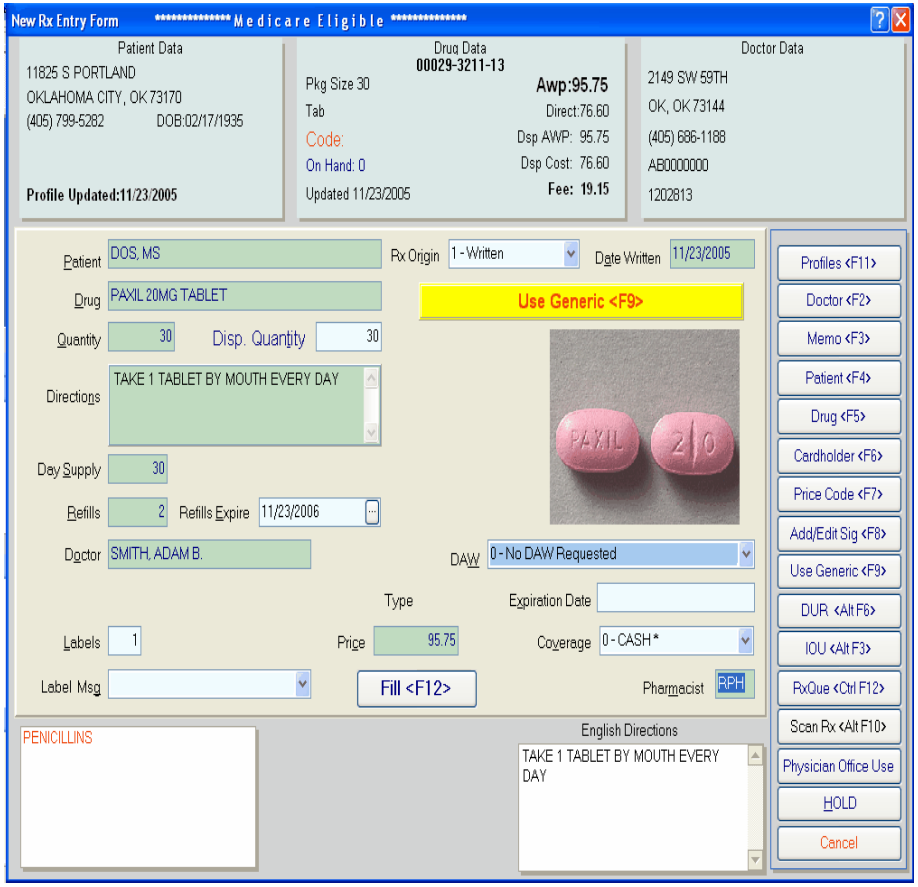
Refill Records

- Advantages
  - Objective
  - Standardized data
  - Identify patients who fail to refill medication
  - Not invasive
  - Inexpensive
- Disadvantages
  - Possible misinterpretation of use when changes made to dosage
  - Assumes filled prescriptions are taken
  - Assumes all sources of medication are captured
  - Only useful for long-term medication
  - Increased complexity when using records from multiple pharmacies



Chisholm et al. *Transplantation* 2000;70:1240-44; Chisholm et al. *Clin Transplant* 2001;15:330-36; Chisholm et al. *Patient Educ Couns* 2005;59:13-20; Hill J. *Musculoskeletal Care* 2005;3:143-56; Liu H, et al. *Ann Intern Med* 2001;134:968-77; Modi AC, et al. *Diabet Med* 2006;5:177-85; Partridge AH, et al. *J Natl Cancer Inst* 2002;94:652-61.

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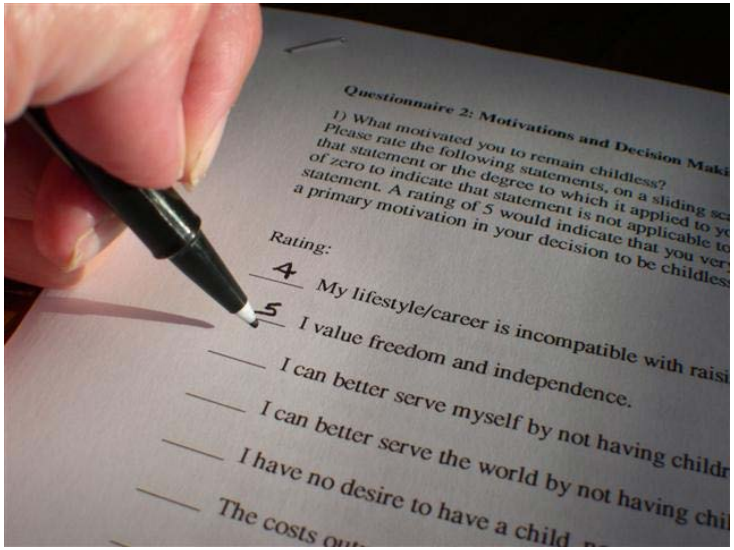
Medication Possession Ratio or Proportion of Days Covered

- **Medication Possession Ratio (MPR)** and **Proportion of Days Covered (PDC)** are the two most common formulas used to estimate patients' adherence to chronic medications. Both formulas use prescription fill data to calculate the percentage of days for which the patient has medication on-hand to take for their chronic conditions.
- Examples of adherence measures for diabetes and cardiovascular medications can be obtained from the Pharmacy Quality Alliance (PQA) at: www.PQAalliance.org
- Optimal MPR is not known for any immunosuppressant.

Self Reports

- Advantages
  - Simple
  - Quick
  - Inexpensive
  - May provide information that explains variability in pharmacoadherence patterns and/or clinical response to medication
- Disadvantages
  - Overestimate pharmacoadherence
  - Patients may provide socially acceptable responses
  - Limited patient recall (impact of time)
  - Diaries may be burdensome/not returned/not completed
  - Tend to be done at time of clinic visit when pharmacoadherence generally increases (bias)



Bennett Johnson S. *Diabetes Care* 1992;15:1658-67; Butler et al. *Transplantation* 2004;77:786-89; Chisholm et al. *Patient Educ Couns* 2005;59:13-20; Farmer KC. *Clin Ther* 1999;21:1074-90; Hill J. *Musculoskeletal Care* 2005;3:143-56; Liu H, et al. *Ann Intern Med* 2001;134:968-77; Modi AC, et al. *Diabet Med* 2006;5:177-85; Prado JC Jr., et al. *J Hum Hypertens* 2007;21:579-84; Schlenck EA, et al. *J Gerontol Nurs* 2004;30:33-43.

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Clinician Reports

- Advantages
  - Simple
  - Quick
  - Inexpensive
- Disadvantages
  - May be influenced by interactions with patients and by patient therapeutic outcomes
  - Tends to underestimate non-adherence

Bennett Johnson S. *Diabetes Care* 1992;15:1658-67; Byerly MJ, et al. *Psychiatr Serv* 2007;58:844-47; Chisholm MA, et al. *Transplantation* 2007;84:1145-50; Miller LG, Hays RD. *HIV Clin Trials* 2000;1:36-46; Rand CS, Wise RA. *Am J Respir Crit Care Med* 1994;149:569-76.

Table 1. Methods to monitor immunosuppressant adherence in transplant recipients (7,17-18).			
		Advantages	Disadvantages
DIRECT	Observation	• Accurate	• Patient able to alter data (e.g., pill cheeking) • Routine use in clinical practice is impractical
	Measurement (i.e., blood, urine) of drug, metabolite, or biological marker	• Objective	• Increased costs • Patient factors may impact results (e.g., metabolism)
	Ingestible Sensor System	• Objective • Accurate • Confirms medication ingestion • Able to track ingestion of multiple medications taken at the same time	• Increased costs • System usability requires mobile telephone service • Need for sensor applied to the skin • Potential for skin reactions
INDIRECT	Patient questionnaires, interviews, self-reports	• Easy to use • Low costs	• Subjective • Relies on patient recall • Patient able to alter data
	Patient diaries	• Simple • Inexpensive	• Subjective • Relies on patient recall • Patient able to alter data
	Pill counts	• Objective • Easy to perform	• Does not confirm medication ingestion • Patient able to alter data • Does not provide information on dose, timing, or drug holidays
	Rate of prescription refills	• Objective • Easy to obtain data	• Refill rate does not necessarily equal ingestion rate • Difficult to perform when patient uses multiple pharmacies
	Electronic monitoring	• Objective • Precise • Effective in controlled research setting	• Increased costs • Data download required • Does not confirm medication ingestion • Interventions in real time unlikely • Selection bias • Routine use in clinical practice is impractical

Adapted from Kaiser T and Alloway R. Clinical Transplants 2015, Chapter 27 p275-284

Quantitating Non-Adherence

- There are many measures of pharmacoadherence applicable to transplantation
  - Direct observation
  - Drug concentration monitoring
  - Electronic monitoring
  - Refill records
  - Self reports
- There is no single perfect measure of pharmacoadherence
- Multiple measures of pharmacoadherence are optimal to provide an accurate adherence assessment

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Prevalence of Nonadherence after Organ Transplantation

Mary Amanda Dew, Ph.D.

Professor of Psychiatry, Psychology, Epidemiology, Biostatistics
and Clinical and Translational Science

Director, Clinical Epidemiology Program, Western Psychiatric Institute and Clinic

University of Pittsburgh School of Medicine and Medical Center
Pittsburgh, PA, USA

Prevalence of nonadherence post-transplant

Why does it matter what the exact prevalence is?

- In order to estimate how likely transplant recipients are to become nonadherent to one or more components of the medical regimen.
- In order to design and test interventions that are targeted to the appropriate transplant recipients and are cost-effective.

Areas of post-transplant adherence that can affect health outcomes

Taking immuno-suppressants

Exercise & Diet

Taking other medications

Substance use

Clinic appointment attendance

Other lifestyle behaviors (e.g., sun exposure)

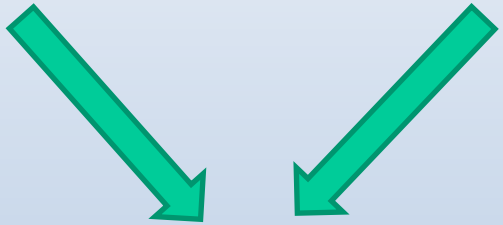
Blood work & tests

Home self-monitoring (bp, temp, etc.)

Two ways to study post-transplant adherence

1. Quantitative measurements
   (e.g., patient-reported levels, biologic measures, other behavioral/observational measures)

2. Qualitative measurements
   (e.g., patient descriptions of how they manage the regimen & what problems they experience)



- Many studies within each of these categories
- Several definitive systematic reviews of these literatures provide summaries of the evidence

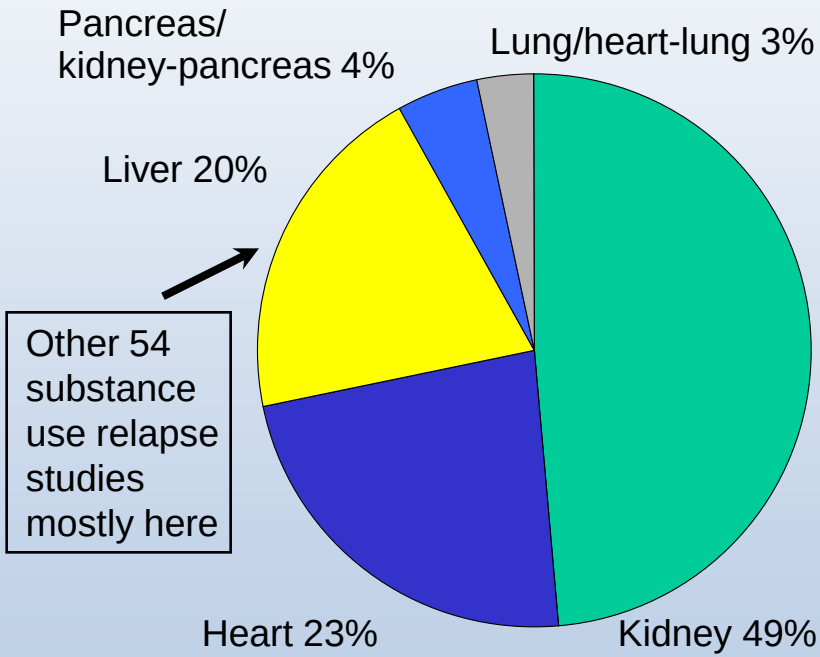
1. Quantitative data: 3 major systematic reviews (meta-analyses)

- Focus on nonadherence prevalence rates in each of multiple areas of the post-transplant regiment
- Considered all types of solid organ transplantation
- Samples: Studies since 1981, including
  - 147 studies, adult general transplant samples
  - 54 studies, adult recipients with substance abuse/dependence histories
  - 61 studies, pediatric general transplant samples

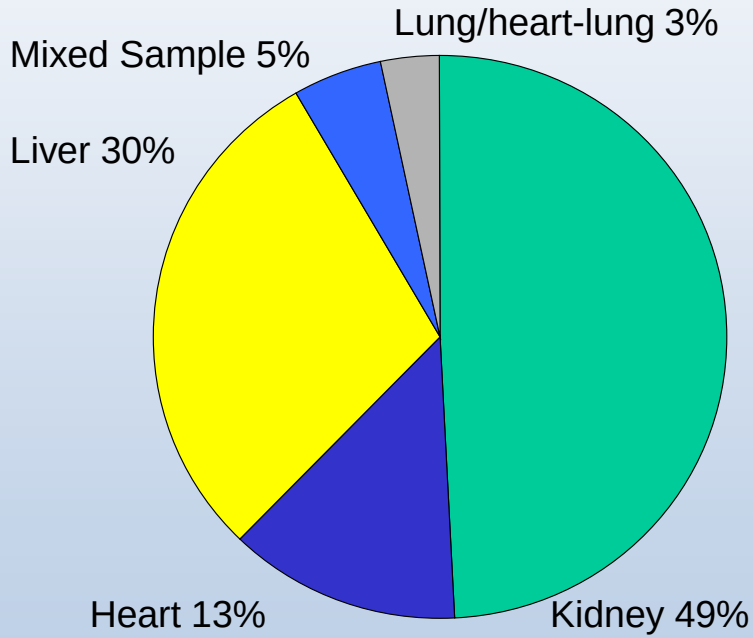
Dew et al., *Transplantation*, 2007, *Liver Transplantation,* 2008; *Transplantation*, 2009

Distribution of studies across areas of transplant

147 studies of adults

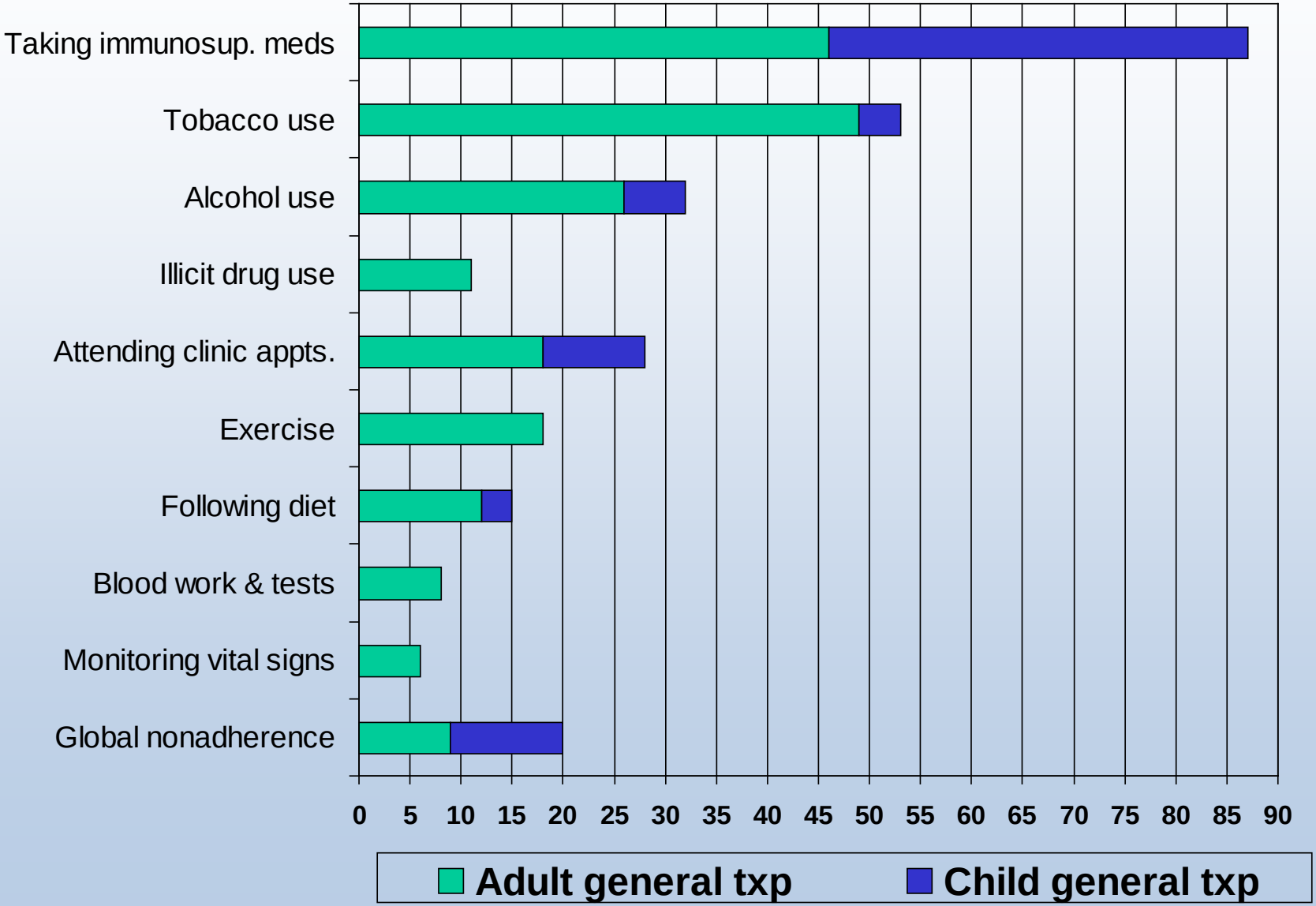


61 studies of children

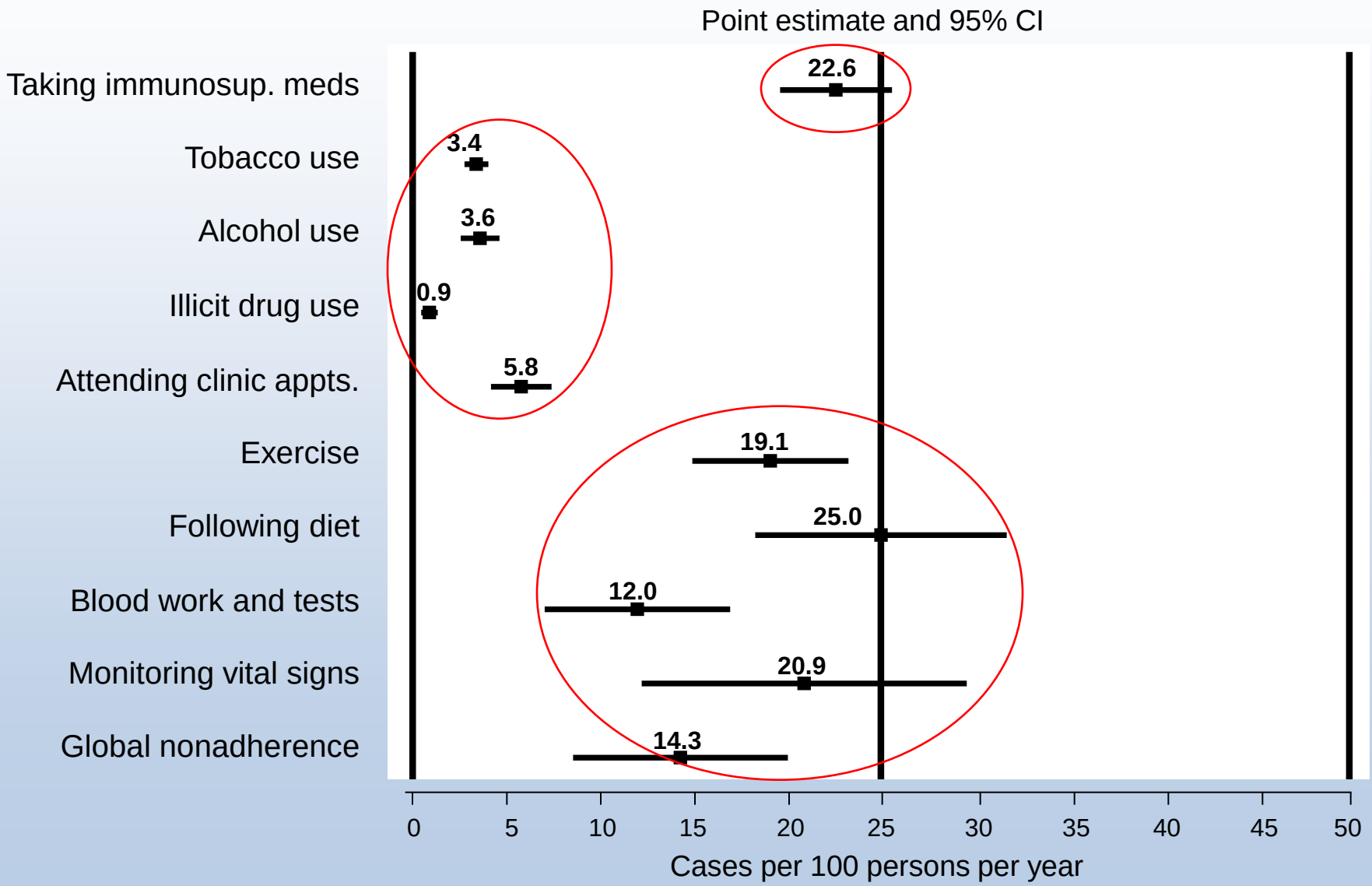


Dew et al., *Transplantation*, 2007, *Liver Transplantation,* 2008; *Transplantation*, 2009

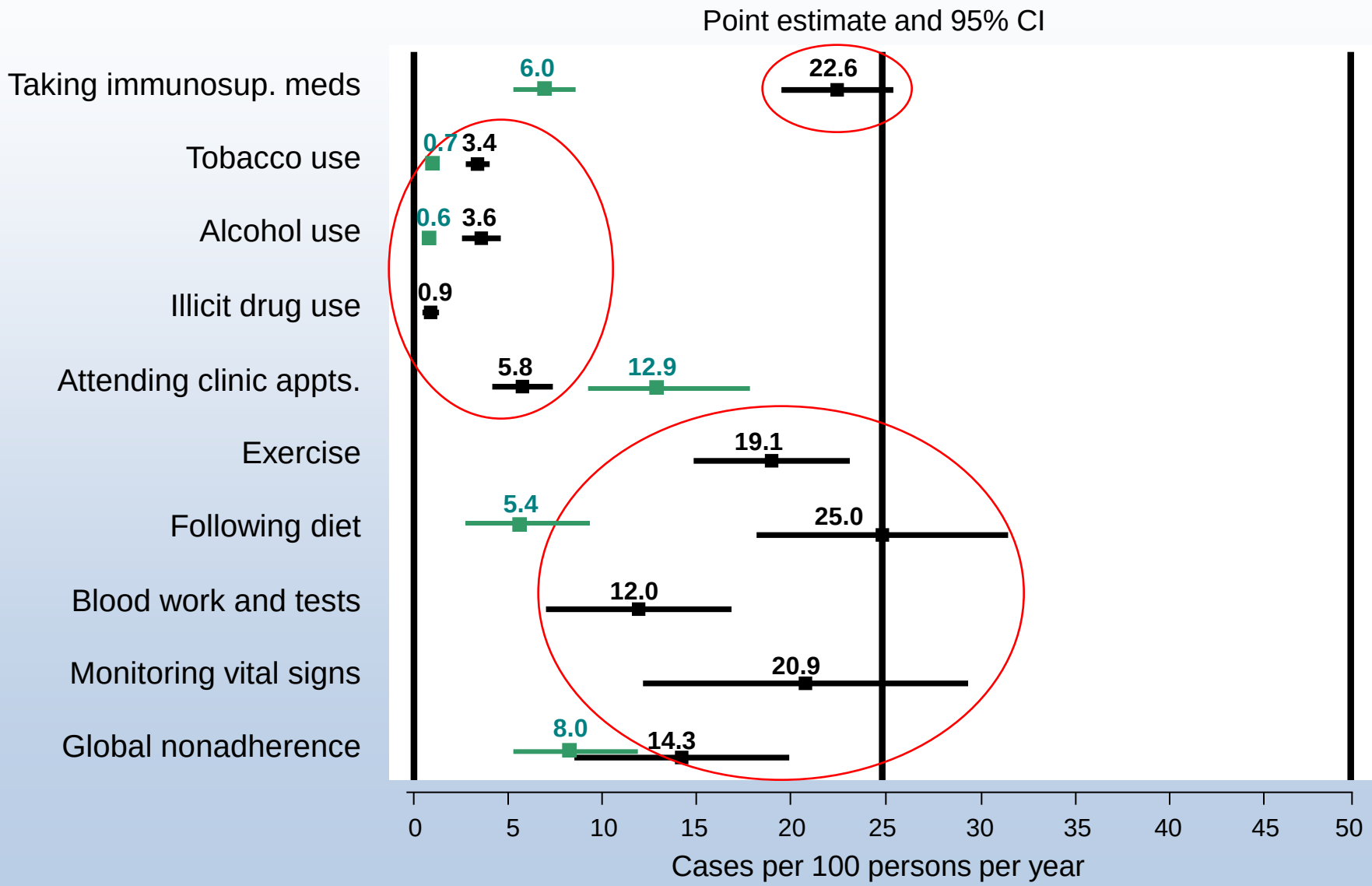
Numbers of studies examining each nonadherence outcome



Results: Average nonadherence rates in 10 outcome areas



Results: Average nonadherence rates in 10 outcome areas



Results: Predictors/correlates of nonadherence after transplant

Adults

Immunosuppressant nonadherence

- Nonwhite ethnicity
- Poorer social support
- Poorer perceived health

Substance use nonadherence

- Pre-transplant substance use

Relapse to alcohol use

- Poorer social support
- Family history, alcohol abuse
- Pre-tx alcohol abstinence ≤ 6 mos

Diet, exercise, healthcare follow-up

(no factors emerged)

Children

Nonadherence to any area of regimen

- Received public health insurance
- Older age
- Parents' marriage not intact
- Greater time since transplant
- Greater parental distress/burden
- Lower family cohesion/support
- Poorer child behavioral functioning
- Greater child psychological distress

Dew et al., *Transplantation*, 2007, *Liver Transplantation,* 2008; *Transplantation*, 2009

2. Qualitative data: 3 major systematic reviews

- Focus on most common/prevalent experiences and perspectives of transplant recipients in their own words; consideration of the medical regimen as well as other areas post-transplant
- Focus primarily on kidney recipients
- Samples:
  - 50 studies, adult kidney recipient samples (self-management issues)
  - 7 studies, adult kidney recipient samples (medication taking)
  - 18 studies, adolescent transplant samples (experience post-tx)

Tong et al., *J Pediatrics*, 2007; *Nephrol Dial Transplant,* 2009; Jamieson et al., *Am J Kid Dis,* 2016

Results: Common self-management themes

1. Empowerment: *gaining a sense of control over the regimen*

I discovered the possibility of maintaining control, even if you ask for help.

I'm good at planning ahead…I got this chart, this box I refill once every week.

2. Fear of consequences: *fear of graft loss and meds' adverse effects, defining acceptable risks*

I do think we walk on a knife-edge all the time and you can just fall off it [and lose the transplant].

To find out that I had cancer [due to the meds] would probably be more devastating to me than having kidney failure.

Results: Common self-management themes

3. Managing regimen demands: *forgetfulness, side effects, lifestyle disruptions*

…The hardest thing is if you are someplace new or doing something new and remembering to take your medicines.

I really had to push for a [medicine] change because the doctors didn't think [hair loss] was kind of a relevant thing to worry about.

4. Overmedicalizing life: *fatigue at being a patient; self-management burn-out*

You can't call it living a life…I'm still living like a patient. I can't do the stuff I wanted to…I'm just dead!

I was doing really well…I started thinking…I don't need all those pills…I just stopped taking them [little by little]. I was tired of them, they made me feel like a sick person…Then, of course, I went into rejection.

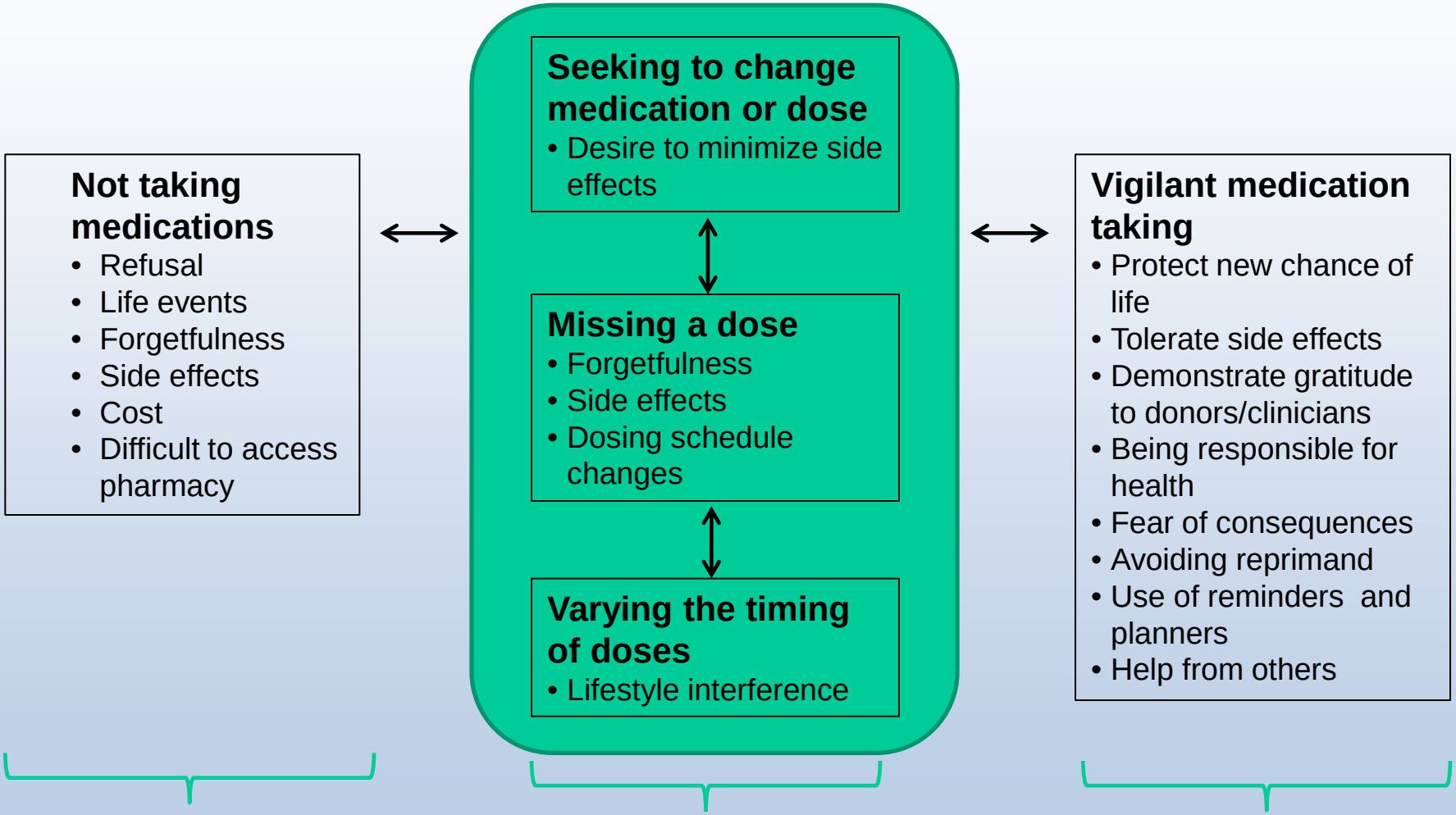
Results: Common self-management themes emerging

5. Social accountability and motivation: *indebtedness to the donor, gratitude to the medical team*

This kidney was given to me by my wife. I have an obligation to take good care of this kidney.

You can't forget [your meds]. I'd be afraid to face my [doctor] if I did that. They don't say much but it's the way they look at you. You know they are disappointed in you.

Results: Integration of medication-related themes voiced by recipients



Adapted from Tong et al., *Nephrol Dial Transplant* 2011

General Conclusions

- ✓ Nonadherence occurs in relatively large proportions of transplant recipients
- ✓ Among the highest rates for adults: immunosuppressant nonadherence
- ✓ Among the highest rates for children: clinic appointment and test nonadherence
- ✓ Nonadherence is modestly associated with patient psychosocial factors in quantitative studies…*but* a limited range of such factors have been considered
- ✓ Patients most commonly voice (a) the need to take control of the regimen but not let it control them; (b) concerns about adverse effects; and (c) motivations for following the regimen
- ✓ Listening to what patients tell us may generate new ideas for ways to help them

Pittsburgh at dusk

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Adherence to Immunosuppressive Medications in Pediatric and Adolescent Transplant Recipients : A Pediatric Nephrologist's View

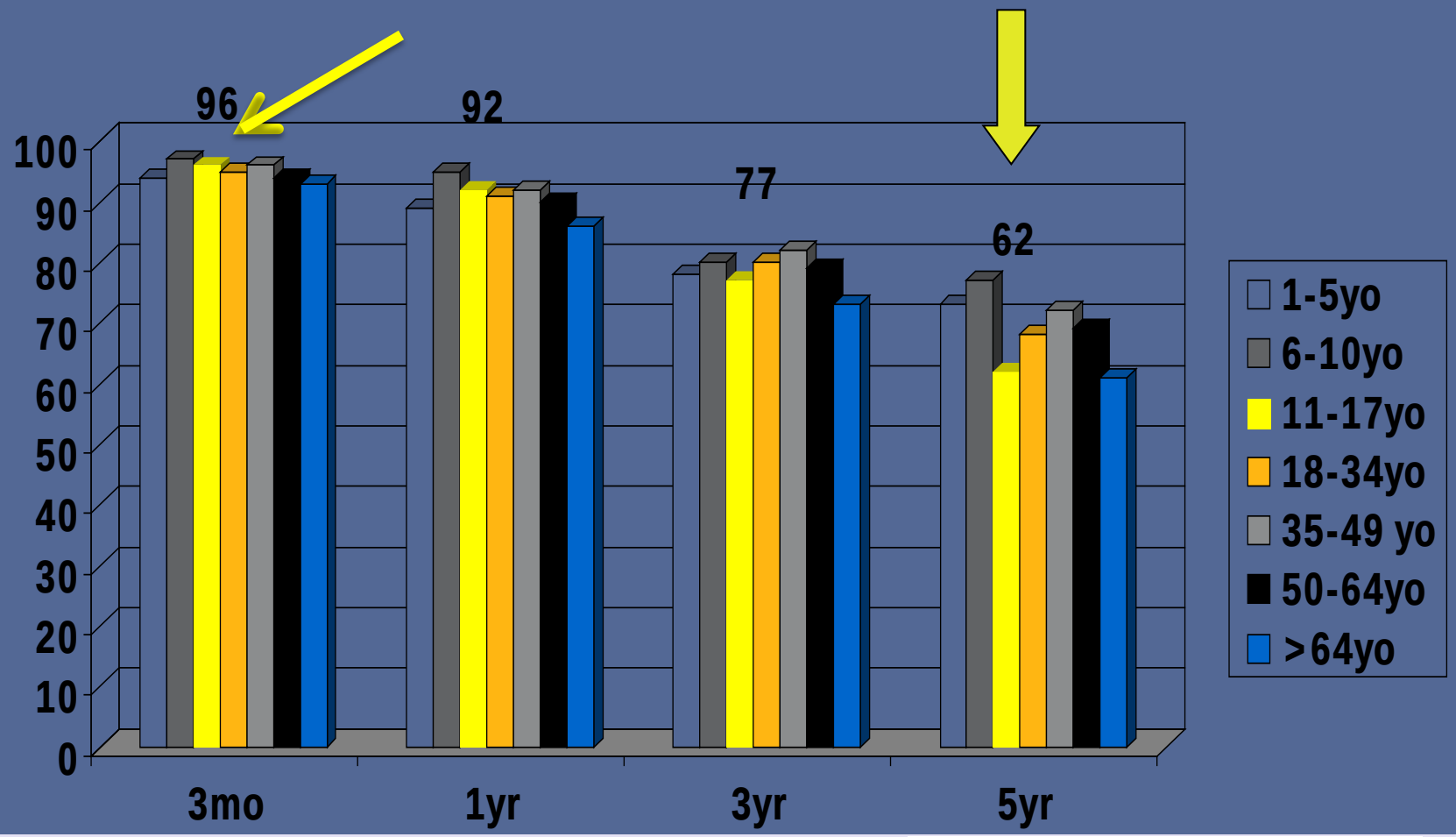
Robert Ettenger MD

Distinguished Research Professor, Emeritus

Department of Pediatrics, Division of Nephrology

Note: Emphasized points are in **RED**

Scope of the Problem:
Adolescents have the best one year outcome and the *worst five year outcome of all age groups*



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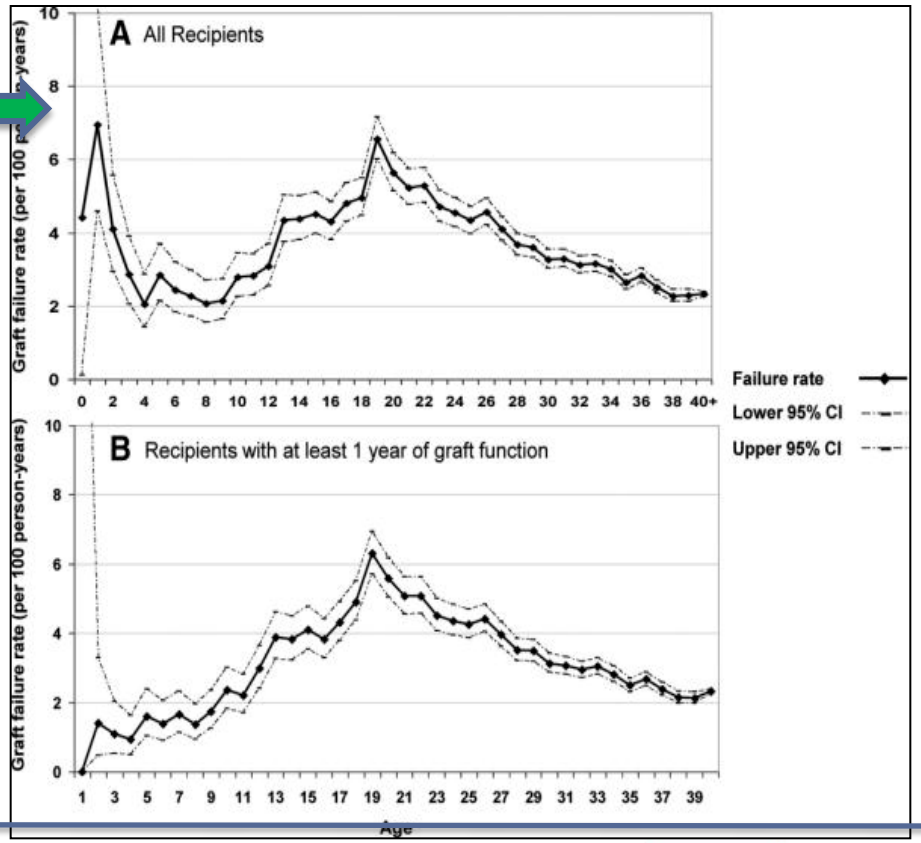
Scope of the Problem in Kidney Transplantation

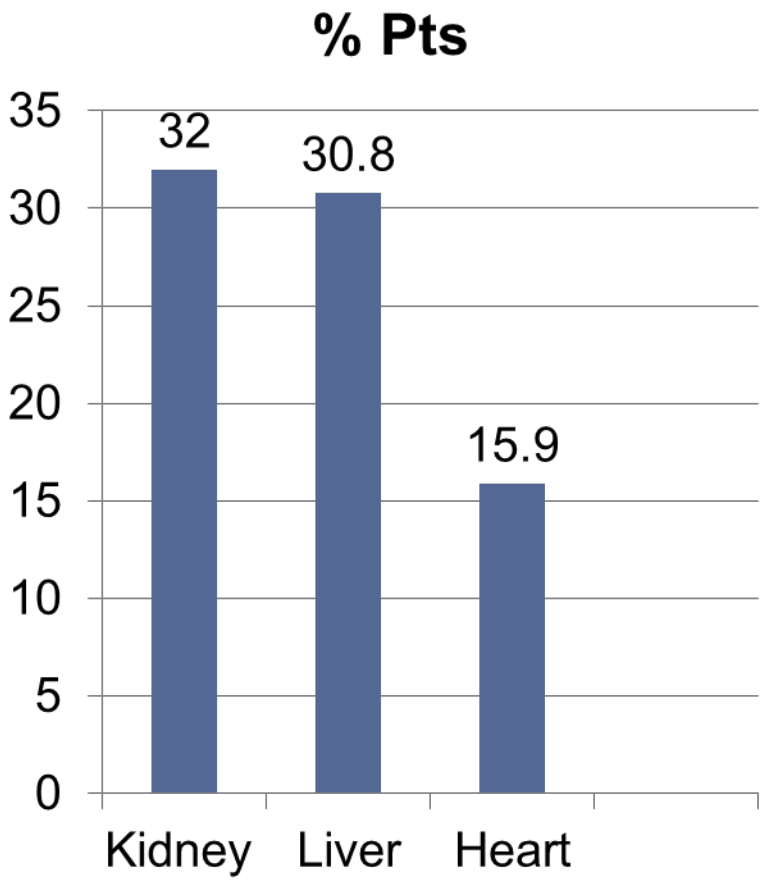
- **After the First Post-Transplant Year, Adolescents, Have the Highest Graft Failure Rate Of Any Age Group**
- **Graft Failure is most often due to antibody mediated rejection (ABMR), likely secondary to medication nonadherence**
- **The Donor Specific Antibodies generated during adolescent graft failure due to noncompliance lead to prolonged waiting times as young adults and poorer subsequent re-transplant outcome**

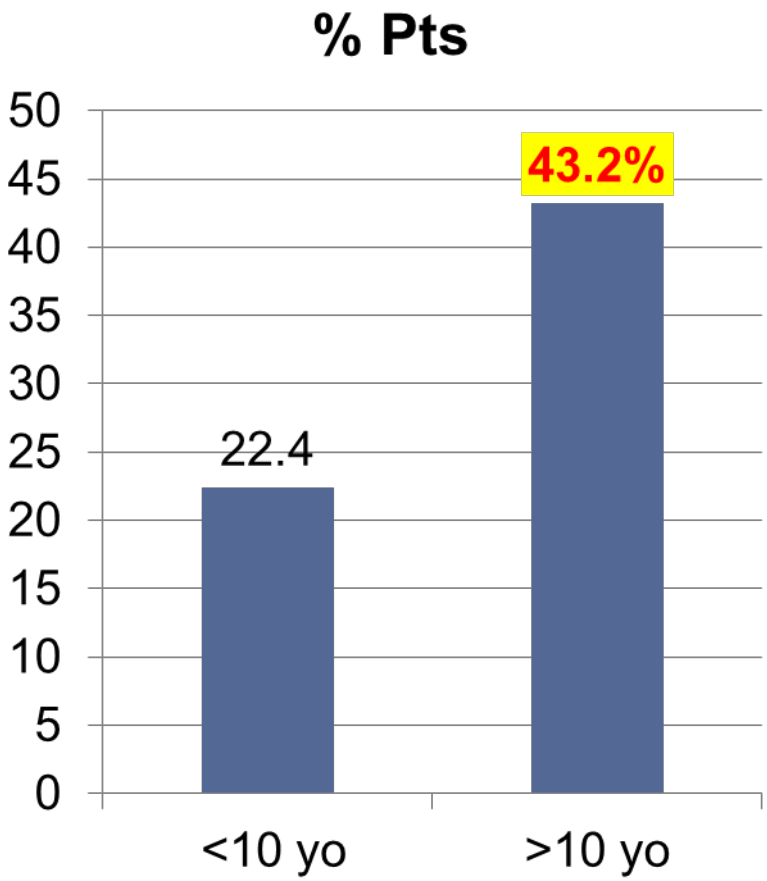
- Foster et al, Transplantation 2011



Prevalence of Medication Nonadherence in Pediatric Transplant Recipients

(Reviewed in Ettenger & Stuber : Nonadherence, Psychosocial Adaptation and It's Effects in Pediatric Transplantation: in Textbook of Organ Transplantation ; Wley 2014)





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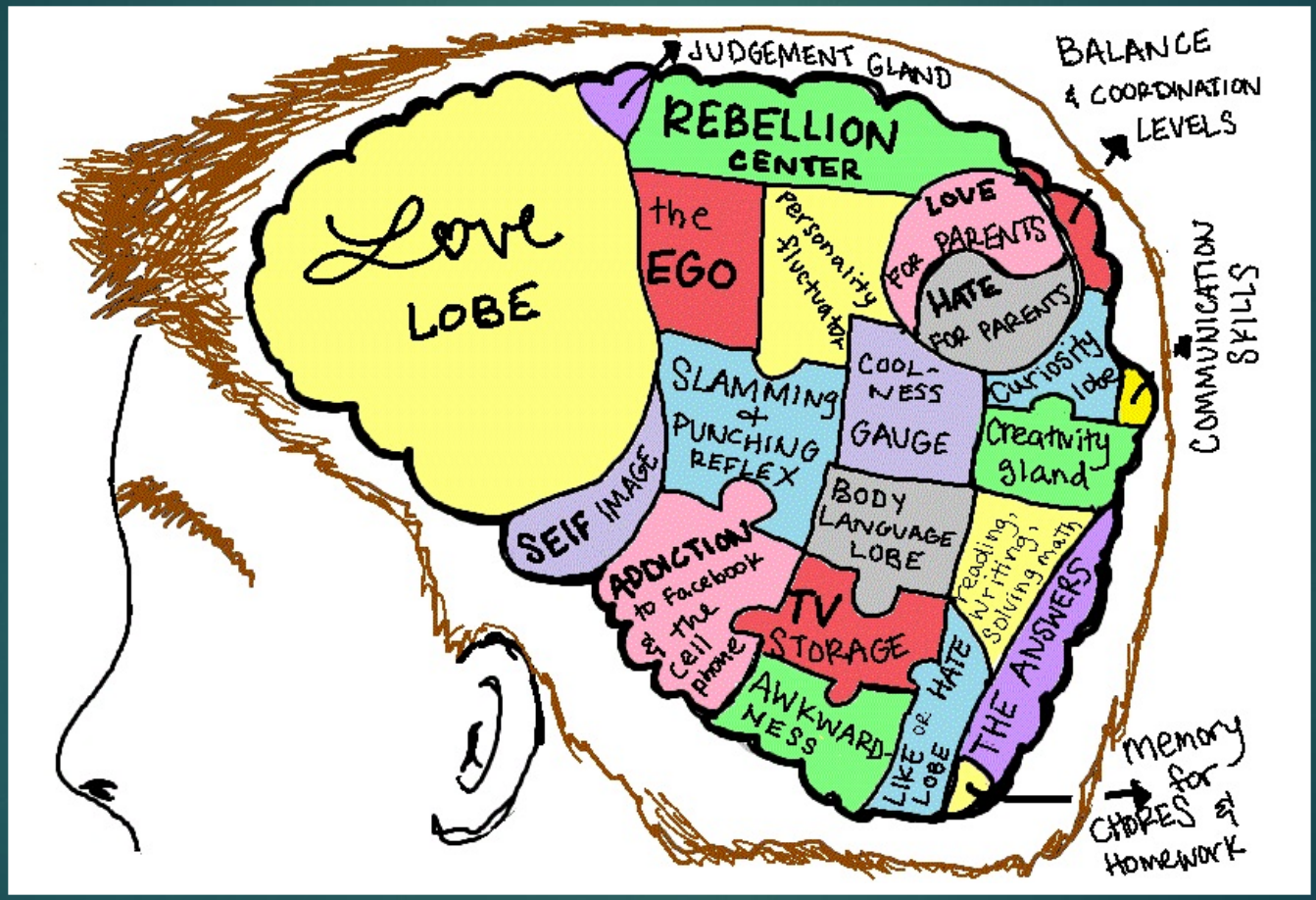
Selected Patient-Related Factors That Associate with Medication Nonadherence in Pediatric / Adolescent Transplant Recipients

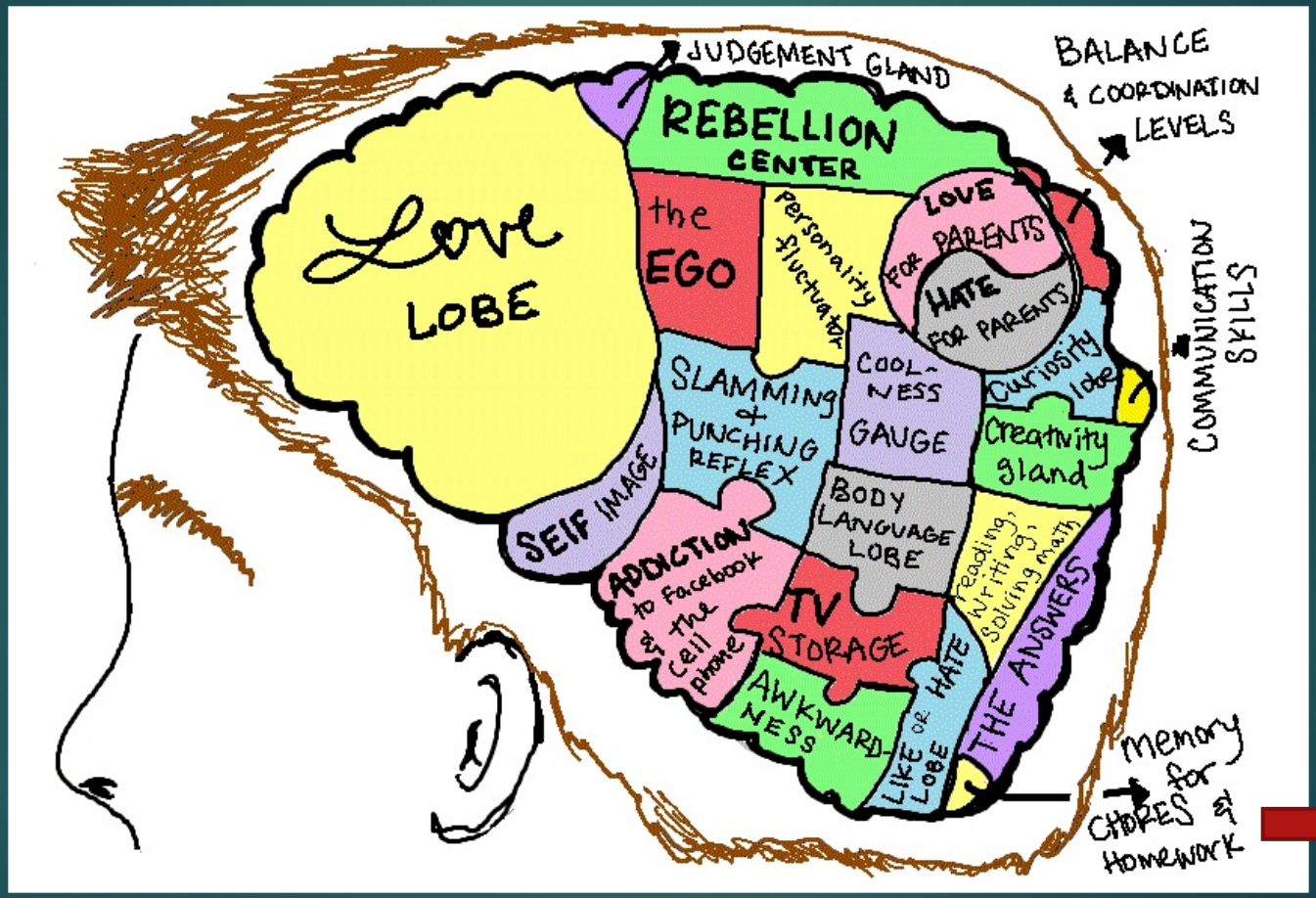
(Adapted from Ettenger & Stuber : Nonadherence, Psychosocial Adaptation and It's Effects in Pediatric Transplantation: in Textbook of Organ Transplantation ; Wiley 2014)

- Poor Knowledge of Medications
- Low self-esteem
  - Poor Body Image
  - Not liking to carry medications with them
- Forgetfulness : "busy life style"
- Developmental delay : either organic or related to effects of chronic illness
- Psychological
  - Depression / Anxiety
  - PTSD
  - Anger
  - Denial
  - Poor Coping Mechanisms
- Social
  - Poor Social Skills / problems with social adjustment
  - Deficient Social Support
  - Reluctance to admit to friends / peers that patient has a transplant

Unique Psychosocial and Developmental Aspects of Adolescence



Unique Psychosocial and Developmental Aspects of Adolescence



Some Unique Psychosocial and Developmental Aspects of Adolescence that Impact Medication Adherence

Three prominent characteristics of adolescent behavior	• Risk Taking • Increased Sensation Seeking • **Move away from patients to greater peer affiliation**
Cognitive and emotional neuronal networks mature at different rates	• Limbic (aka Emotional) circuitry develops earlier • Prefrontal lobe circuitry develops more slowly • Necessary for executive functioning : **abstraction, long-term planning, attention, response inhibition etc**.
Need for separation and individuation : experimenting to see which values of patients etc. they will adopt	• Questioning authority – e.g., what happens if meds missed – if no immediate consequences, ?????? • **The medical team loses credibility when adolescents are non-adherent without consequences**

Barriers to Adolescent Adherence (adapted from Simons & Blount J Ped Psychol 2007)

Barrier Type	Examples	Parent Reported Barriers /N	Parent Reported Barriers/%	Adolescent Reported Barriers / N	Adolescent Reported Barriers/%
		76		73	
Forgot/ Distracted	"Not paying attention to how much is left"; "ran out"; "completely forgot"; "doing something else"	13	17%	21	**29%**
Poor Planning / Scheduling Problems	"Keeping 24 hour pill rotation is difficult"; "On weekends, sleeping in"	52	**68%**	42	**58%**
Physical Barriers/ Medication Issues	``Too tired''; ``Nauseous in the morning'';	4	5%	7	10%
Voluntary Resistance/ **Attempts to be Normal**	"When I see my friends don't have to take it, I don't want to take it"; ``Teenage lifestyle''; ``Just not doing it''	7	9%	3	4%

Barriers to Adherence in Adolescent Transplant Recipients

- **Barriers reflecting disorganization / not planning ahead and the desire to avoid having others observe patient taking medications directly related to** (McCormick King et al. J Ped Psych 2014)
  - **Medication nonadherence**
  - **Emotional distress (Anxiety, Depression, Anger and /or PTSD)**
    - **In turn, these are correlated with medication nonadherence**
- **Barriers remain stabile over time** (Simons et al. J Ped Psych 35; 138:2010)
- **Poorer adherence to medication taking associated with**
  - **Adolescent-perceived barriers of Disease Frustration/ Adolescent Issues**
  - **Parent-perceived barriers of Regimen Adaptation/Cognitive Issues**
- **≥ 3 Total Barriers (out of a total of 16) reported by adolescent patients or ≥ 2 Total Barriers reported by patients are sensitive indicators of high risk for medication nonadherence** (Eaton et al J Ped Psych 2015)

Measuring Adherence: Considerations and Challenges in Pediatric and Adolescent Transplant Recipients

Directly Observed Treatment (DOT) can become cumbersome and contentious between parents and adolescents

Success with indirect measurements such as variation in drug levels

- **Liver Transplantation : MALT Study**
- **Renal Transplantation : %CV**

Electronic measurement systems may be limited if adolescents don't want to bring a separate electronic container or "smart" pill box when they are at social gatherings

Self-Report Instruments are limited particularly in adolescents

The MALT Study : Medication Adherence in children who had a Liver Transplant (Shemesh et al ATC 2016 abstr)

- **Medication Level Variability Index (MLVI)**
  - **Calculated from the standard deviation of sequential tacrolimus levels**
  - **A surrogate for erratic medication injection**
  - **A cutoff of > 2 indicates highly fluctuating levels**
- **400 Patients in 5 centers / based on at least 3 drug levels**
- **In adolescents with MLVI > 2 in year 1, 45% develop late rejection in year 2 ; if MLVI < 2, only 8% with late rejection**
- **In adolescents, ROC AUC = 0.78**

Conclusion: A robust predictor of late allograft rejection that could inform interventions to improve outcomes

Instances of CV% Exceeding Cutoffs for Both Sirolimus and Tacrolimus Have Significantly Increased Prevalence of Rejection, DSA and Self-Reported Nonadherence in Adolescent Renal Transplant Recipients (Pizzo et al Ped Nephrol June 10 2016 epub)

Figure 3.

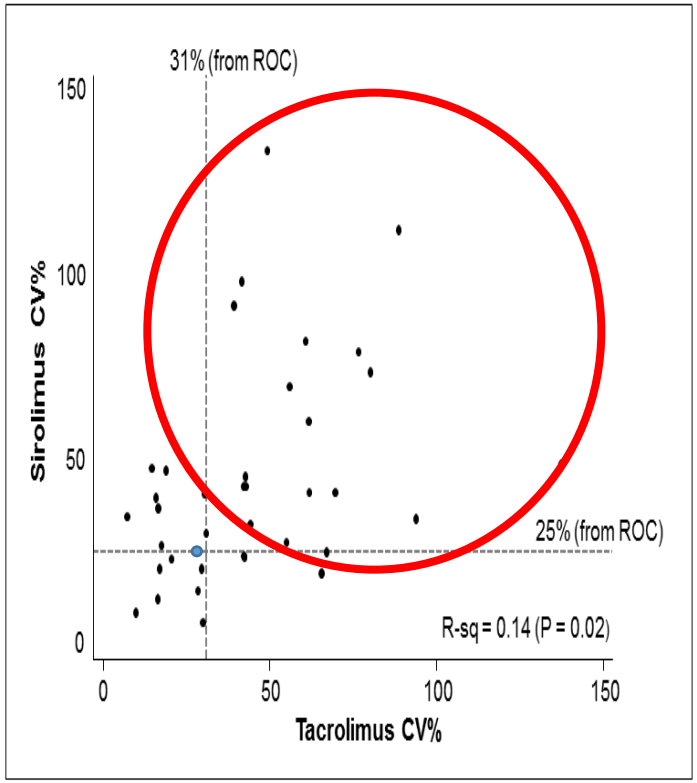
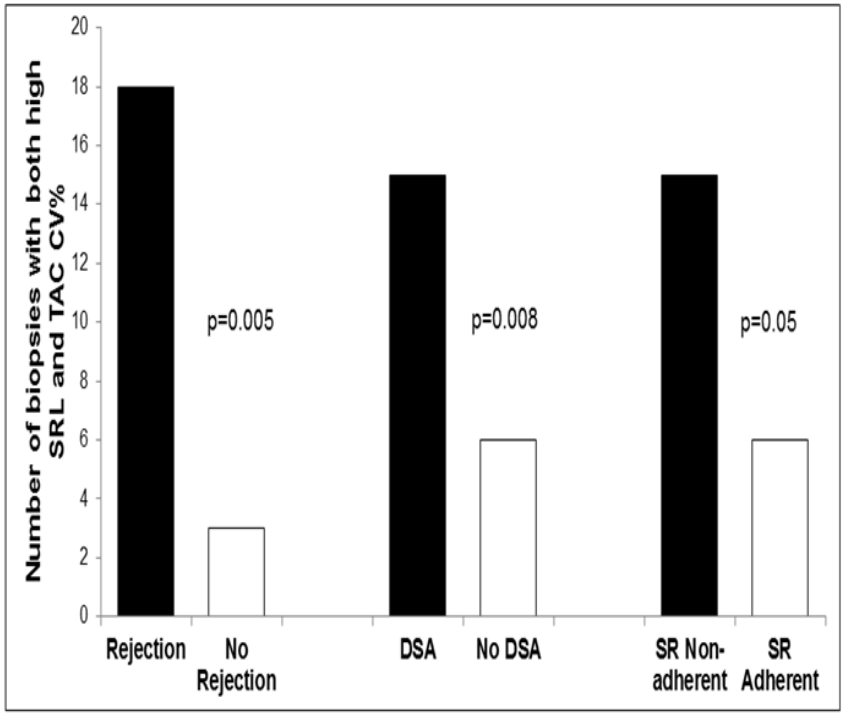


Figure 4.



Panel Discussion Session 1

1. How well do we understand the extent of non-adherence in patients post-transplantation? What type of non-adherence is affecting patient outcomes the most?

2. Are healthcare providers appropriately involved, when it comes to promoting adherence or are they not paying enough attention? What improvements would you suggest?

3. How critical is it to collect adherence data in clinical trials of new drugs or new regimens? What are the consequences of not doing so?

BREAK

U.S. FOOD & DRUG ADMINISTRATION

Scientific Discussion 2: "Interventions to Mitigate Non-Adherence"

Pharmaceutical Dosage Forms to Improve Adherence

What can be done?

What are the limitations?

William E. Fitzsimmons, Pharm.D., M.S.
Astellas Pharma Global Development, Inc.

The opinions expressed herein are my own and not those of Astellas

TABLE 1: MAJOR PREDICTORS OF POOR ADHERENCE TO MEDICINES

Patient-Related Limitations	Barriers to Care or Medicine
Psychological problems, particularly depression	Poor relationship between patient and provider
Cognitive impairment	Missed appointments
Asymptomatic disease	Lack of health insurance
Inadequate follow-up or discharge planning	Cost of copayment or coinsurance
Side effects of medicine	**Complexity of treatment**
Patient lacks belief in benefit of treatment	Access restrictions (e.g., formularies, utilization management)
Patient lacks insight into the illness	

Source: Adapted from L. Osterberg and T. Blaschke. "Adherence to Medicine," *New England Journal of Medicine*, August 2005.

Potential Improved Adherence Through Dosage Form Technology

Sustained-release	Decrease frequency of dosing
Transdermal Patch	Decrease frequency of dosing-avoid oral issues
Melting tablets	Reduce need for water source and addresses swallowing difficulties
Long lasting injections	Greatly reduced dosing frequency but may need to visit the clinic for administration
Chewable tablets	Easier to swallow
Fixed dose combinations	Simplified therapy and reduction in number of tablets/capsules

Wertheimer Al, Santella TM, Finestone AJ, Levy RA. Drug Delivery systems improve pharmaceutical profile and facilitate medication adherence. Advances in Therapy. 2005;22:559-577.

Factors that impact regimen complexity:

- Doses per day
- Pills per day
- Liquids vs. solids
- Instructions for with or without food (empty stomach more complex)
- Refrigeration
- Reconstitution

One tablet/capsule, once a day, regardless of food, taken in the morning

Assumptions:

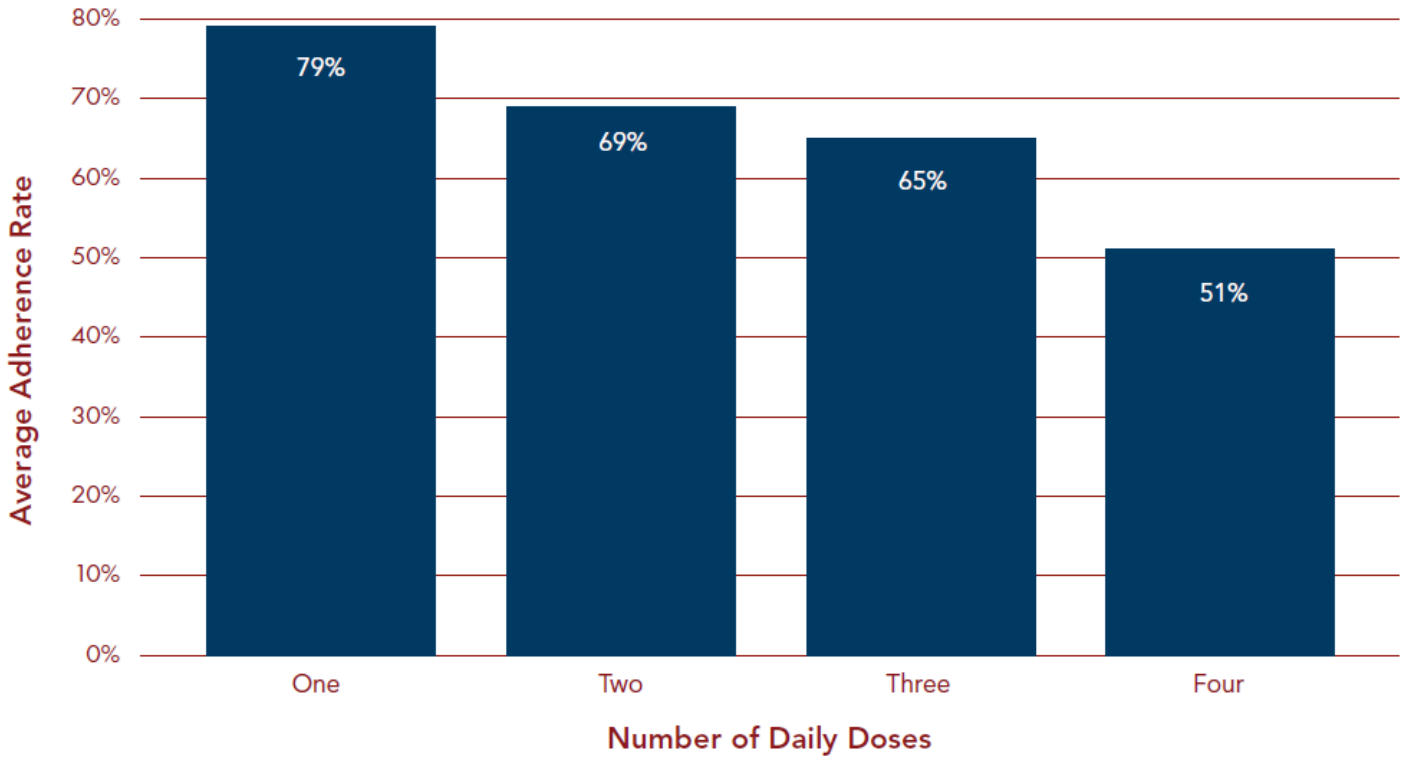
Simplified dosing and reduced regimen complexity should improve adherence even though there are few studies.

Although there are few adherence studies in transplant patients, extrapolation from chronic disease conditions are valid (e.g. diabetes and hypertension are common co-morbidities).

Examples of Dosage Form Technology for Transplant Immunosuppression

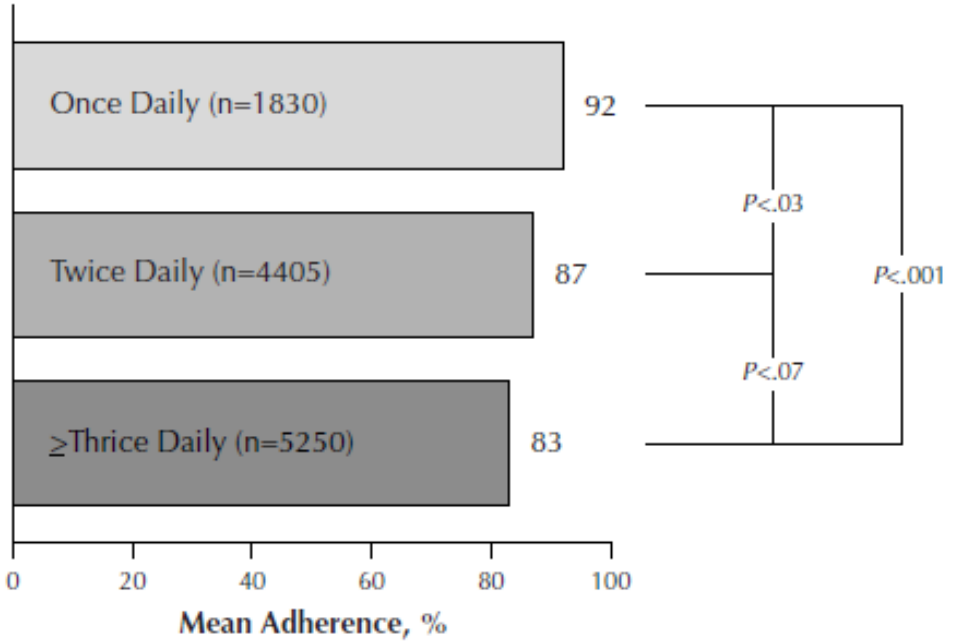
- Long Lasting Injection – Nulojix (belatacept)
- Once Daily Tacrolimus – Astagraf XL and Envarsus XR

FIGURE 3: IMPACT OF DAILY DOSING SCHEDULE ON ADHERENCE



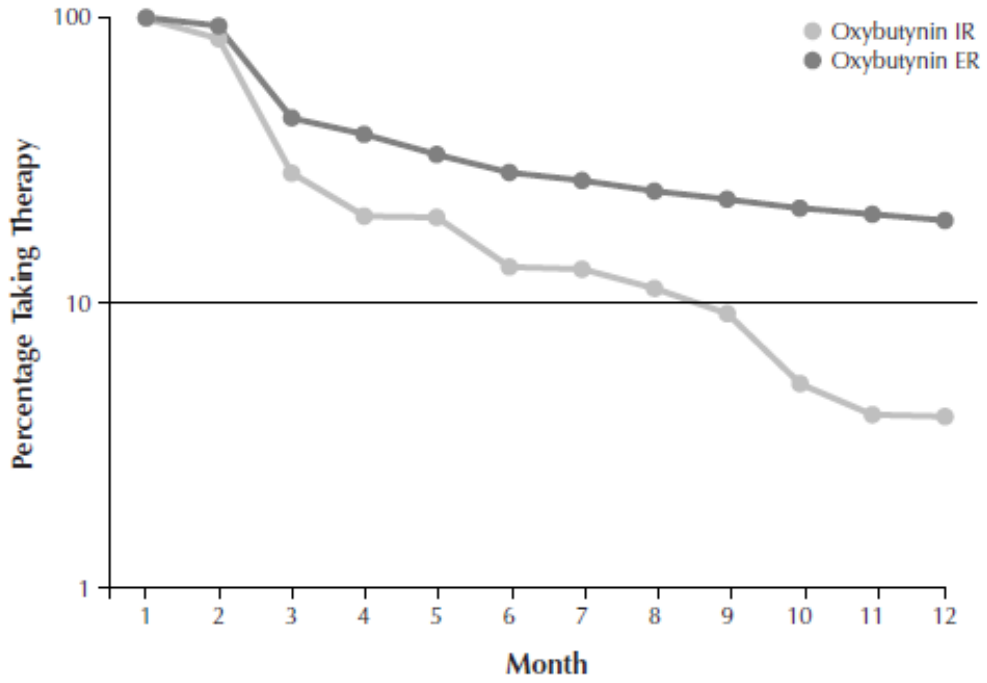
Source: A.J. Claxton et al. "A Systematic Review of the Associations Between Dose Regimens and Medication Compliance." *Clinical Therapeutics*, August 2001.

Fig 2. Dosing frequency and adherence. Meta-analysis of 8 studies involving 11,485 patients with hypertension.



Adapted from Iskedjian M et al. *Clin Ther.* 2002;24:302-316.

Fig 5. Persistence with immediate-release and extended-release oxybutynin formulations for overactive bladder.



IR=immediate release; ER=extended release.

Adapted from Chui MA et al. *Value Health*. 2004;7:366; and Noe L et al. *Manag Care Interface*. 2004;17:54-60.

Improved Adherence to Tacrolimus Once-Daily Formulation in Renal Recipients: A Randomized Controlled Trial Using Electronic Monitoring

Dirk R.J. Kuypers,[1,9] Patrick C. Peeters,[2] Jacques J. Sennesael,[3] Mireille N. Kianda,[4] Bernard Vrijens,[5,6] Paulus Kristanto,[5] Fabienne Dobbels,[7] Yves Vanrenterghem,[1] Nada Kanaan,[8] on behalf of the ADMIRAD Study Team

Transplantation 2013;95:333-40.

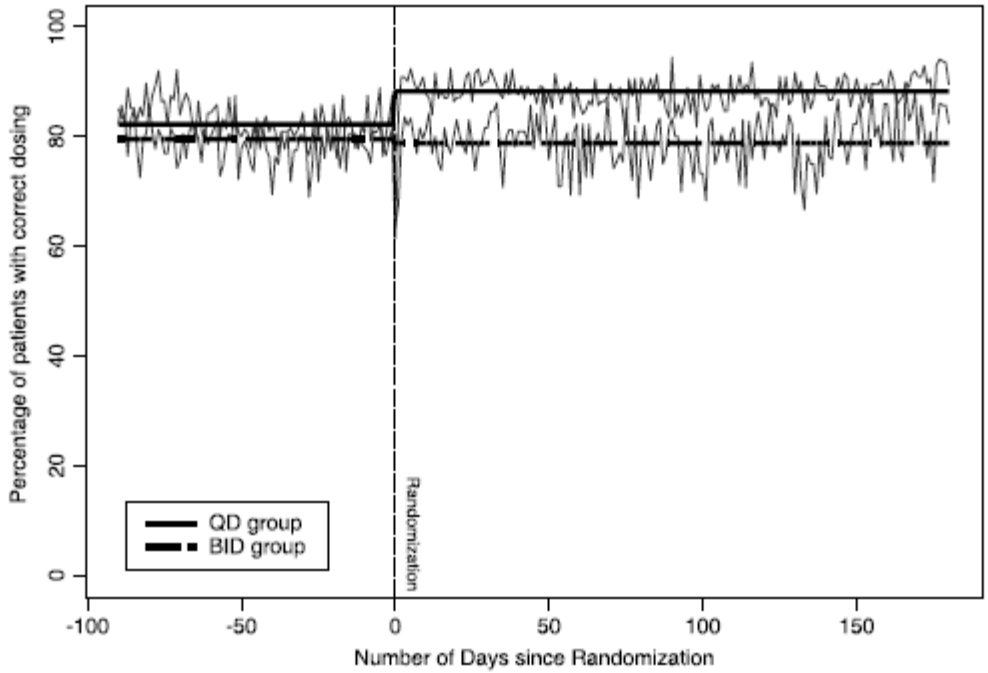


FIGURE 4. The implementation of each dosing regimen represented by the day-to-day percentage of patients with correct dosing relative to patients who were still engaged with the treatment. Correct dosing is defined when the number of the medication intake that day is at least as prescribed. Broken vertical line at time 0 represents time of randomization. The overlaying lines are model-based estimation of the day-to-day percentages.

Transplantation 2013;95:333-40.

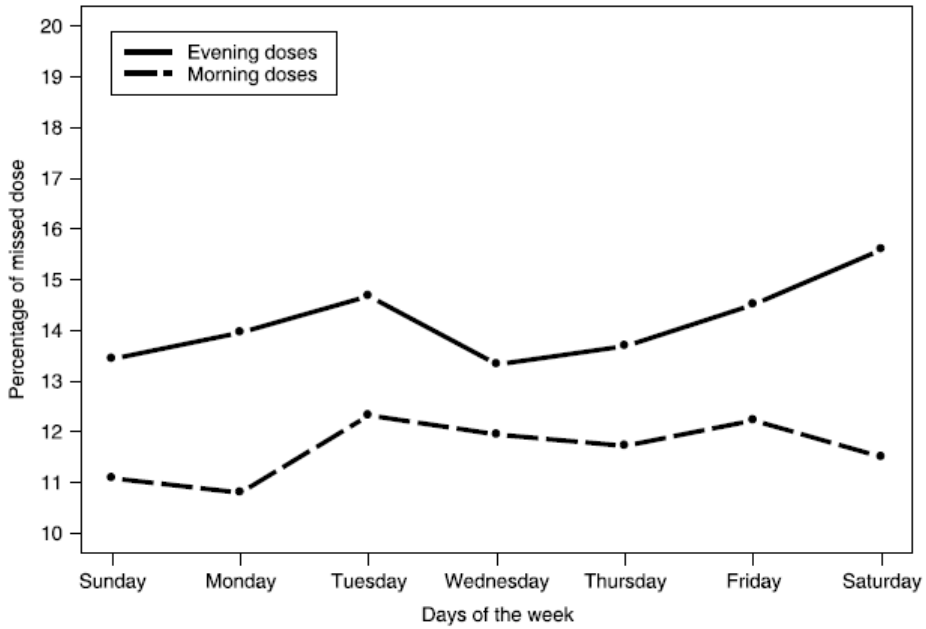


FIGURE 5. Percentage of missed doses by days of the week and morning/evening doses when the patients were prescribed the twice-daily regimen and were still engaged to the treatment.

Transplantation 2013;95:333-40.

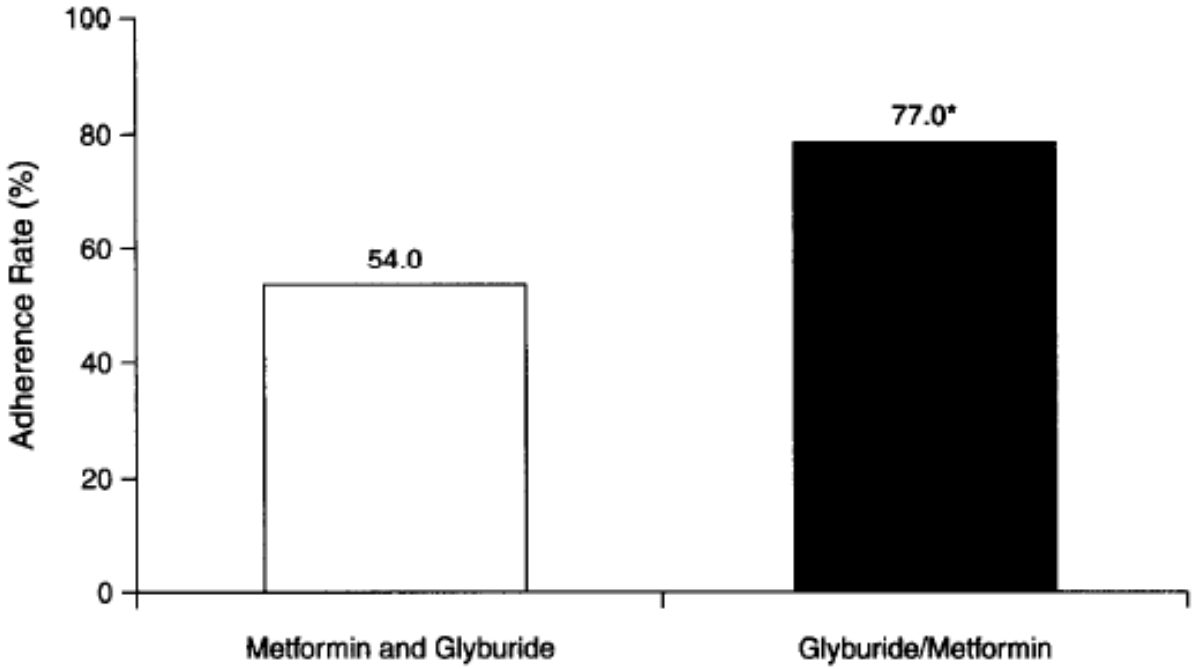
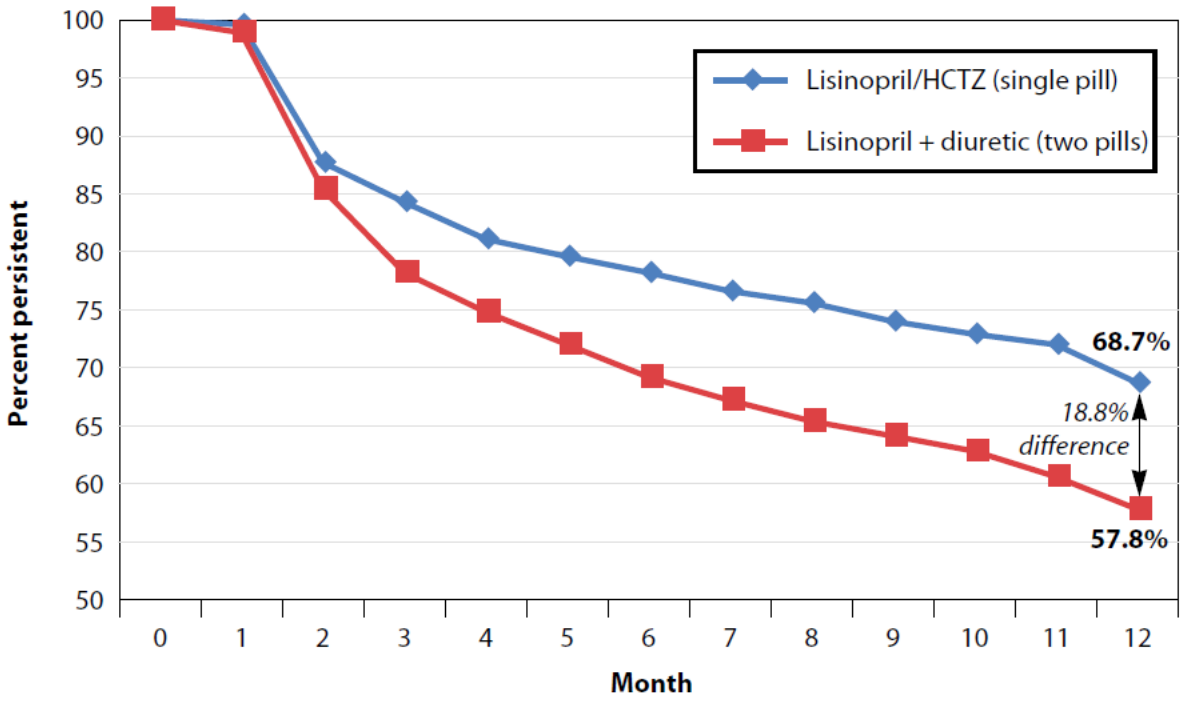


Figure 1. Comparison of adjusted adherence rates in patients receiving metformin and glyburide combination therapy and those receiving fixed-dose glyburide/metformin combination therapy. $^{*}P < 0.001$.

Melikian et al. Clinical Therapeutics. 2002; 24:460-467.

FIGURE 1 Persistence curves for lisinopril and lisinopril/HCTZ*

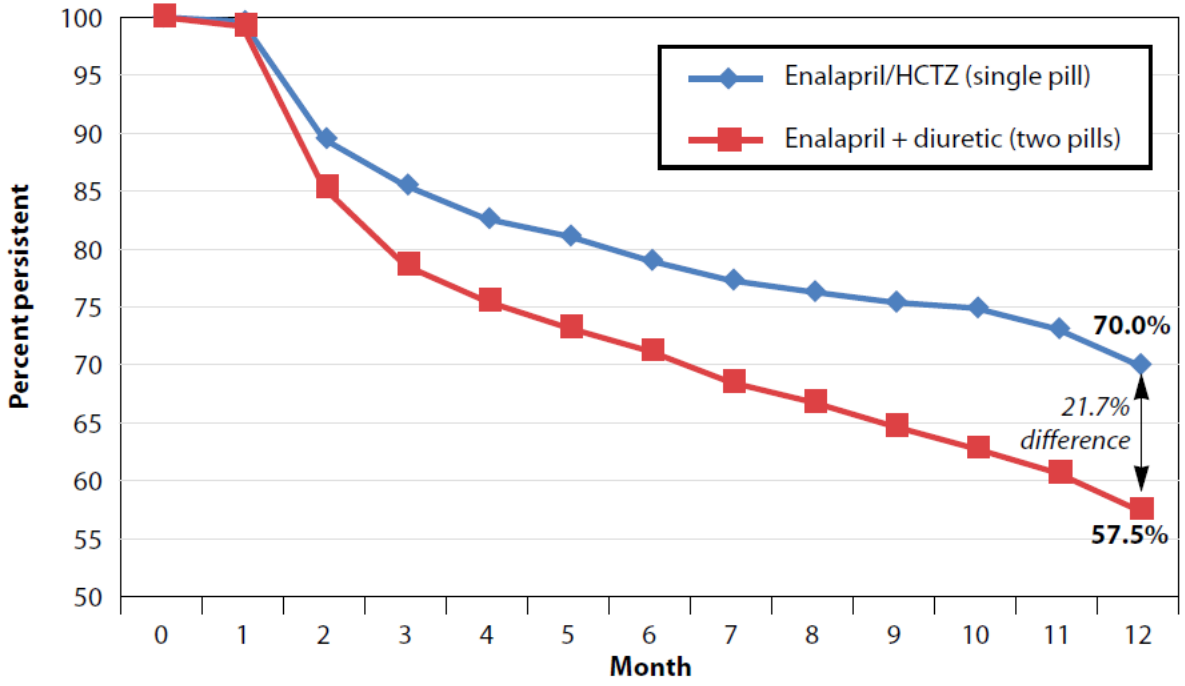


(Lisinopril/HCTZ n = 1644, lisinopril n = 624)

*Statistical significance ($P<0.05$) demonstrated at months 6 and 12 for both comparisons.

Dezii CM. Manag Care. 2001. 9(9 suppl):S2-6.

FIGURE 2 Persistence curves for enalapril maleate and enalapril/HCTZ*



(Enalapril/HCTZ n = 969, enalapril maleate n = 705)
*Statistical significance ($P<0.05$) demonstrated at months 6 and 12 for both comparisons.

Dezii CM. Manag Care. 2001. 9(9 suppl):S2-6.

Limitations:

- Transplant patients are on multi-drug multi-indication regimens.
- Physiochemical and pharmacokinetic characteristics of molecules may preclude patch, or oral bioavailability (eg. biologics).
- Length, cost and complexity of development programs may be a disincentive in a generic environment.

Interventions to Maximize Adherence after Heart, Lung, or Liver Transplantation in Adults

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Challenges to developing adherence-promoting interventions after transplant

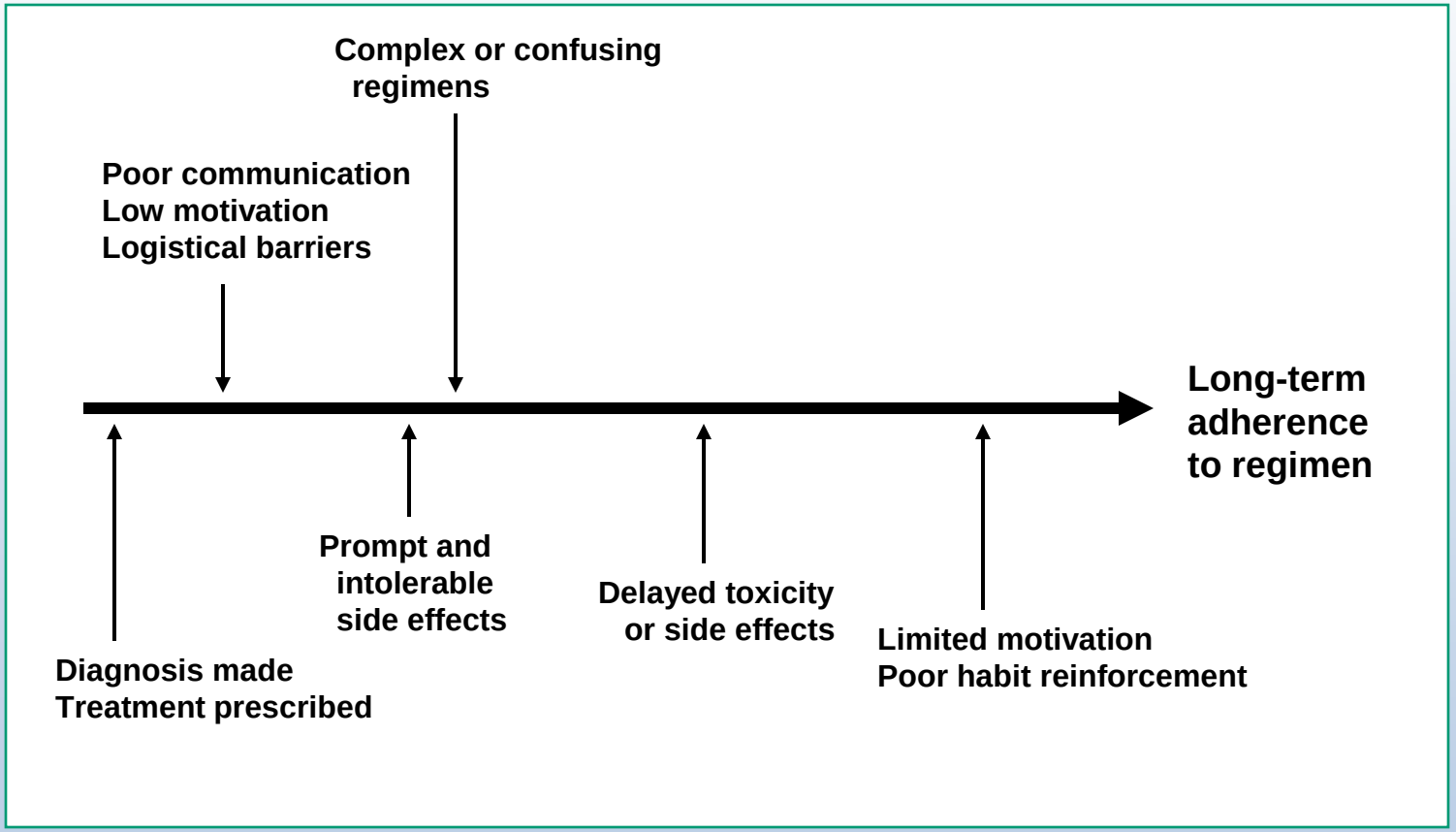
- Long-distance relationship between patients and transplant team
- Limitations of transplant team resources
- Multifactorial nature of medical regimen
- Few interventions tested in transplant populations
  - Lack of powerful interventions in other chronic disease populations

Issues:

- When, where, how to intervene?

When to intervene?

Sequential barriers to adherence



Adapted from Rudd, *Am Heart J*, 1995

Where and how to intervene?

Adherence interventions in chronic disease populations

Modes of offering interventions (the "where")

- Face to face (at discharge, at clinic visits)
- Telephone
- Smartphone apps
- Computer/laptop

Types of interventions tested (the "how")

- Educational
- Behavioral (e.g., problem-solving therapy)
- Psychosocial/Affective (e.g., focus on psychological/social functioning; motivational interviewing)
- Technology-based (e.g., monitoring devices or internet)
- Multicomponent (e.g., educational + behavioral + technology)

Where and how to intervene?

Adherence interventions in chronic disease: Recent meta-analysis findings

- Types of interventions tested are extremely heterogeneous
- Multicomponent interventions appear most effective (but difficult to pinpoint the most potent elements)
- Intervention effectiveness appears to be increased by tailoring (e.g., based on patient needs and dynamic information on patient adherence over time)
- Degree of intervention impact is variable but tends to be small to moderate
- Whether interventions improve clinical outcomes remains unclear
- mHealth strategies appear promising

Strategies to improve adherence after transplant (extrarenal)

Descriptive reports (no formal evaluation)

- behavioral contracting
- behavioral analysis
- mentoring programs and support groups

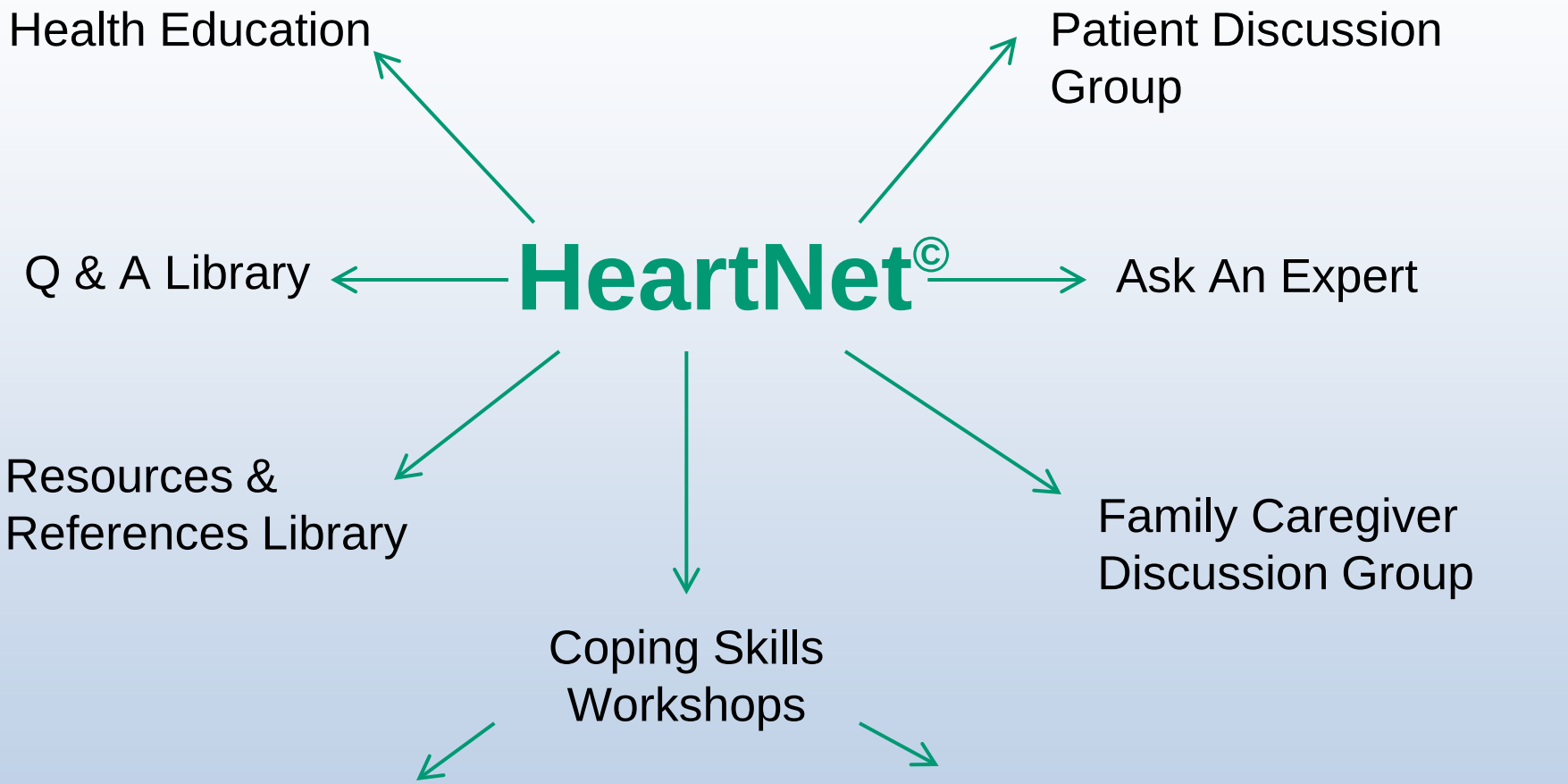
Six intervention trials to date

- Brief medication education programs *(Traiger 1997; Suhling 2014)*
- Electronic platforms with multiple components; focus on self-management of entire medical regimen *(Dew 2004; DeVito Dabbs 2016)*
- Face-to-face multicomponent interventions to improve medication adherence *(Klein 2009; Dobbels 2016)*

No effects

Evidence of effectiveness

1. Internet-based intervention for heart recipients and caregivers



Dew et al., *J Heart Lung Transplant*, 2004

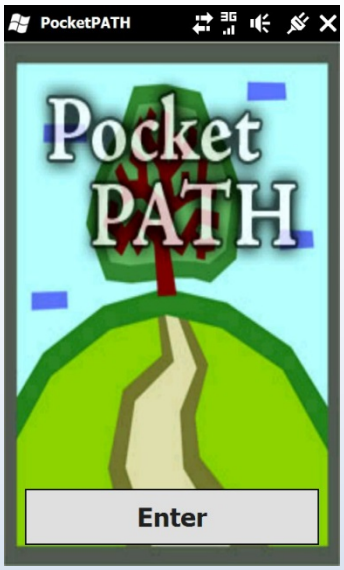
Impact of 4-month HeartNet intervention

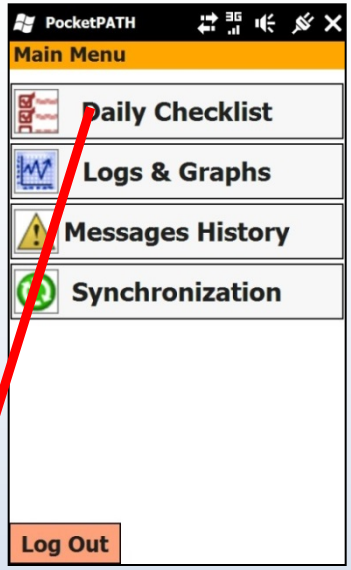
- Transplant recipients' depressive and anxiety symptoms and caregivers' anxiety and hostility symptoms significantly improved relative to controls.
- *Recipient adherence improved in some areas (clinic appointments, blood work, diet) among users of the site's medical regimen workshop.*
- Recipients' QOL in social functioning significantly improved.
- There was a dose-response relationship between frequency of web site use and intervention effects.

Issues: small sample (n=60), historical controls, prospective study but recipients varied in time since transplant; short study period

Dew et al., *J Heart Lung Transplant*, 2004

2. mHealth intervention for lung recipients

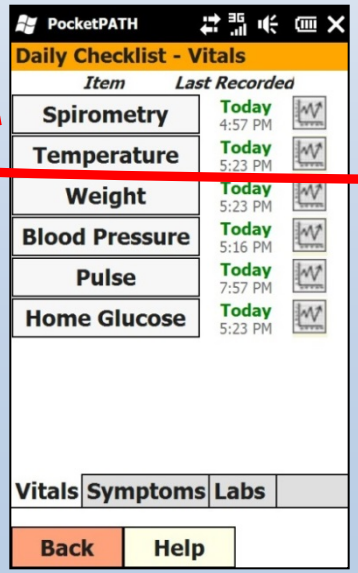


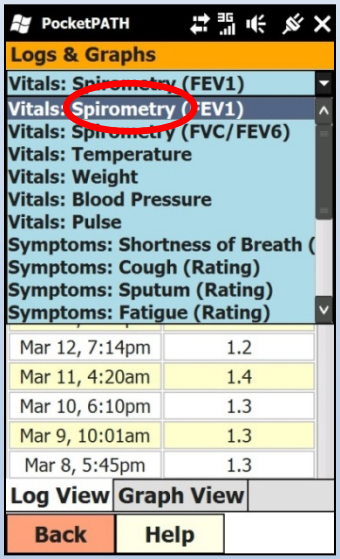


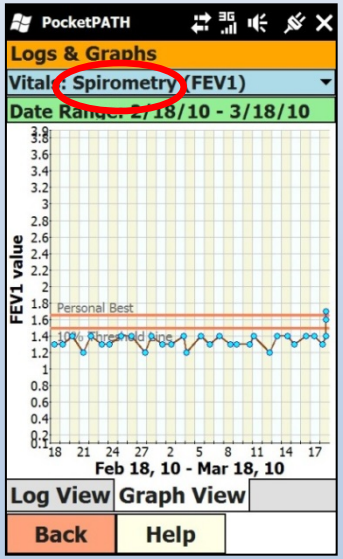
Pocket PATH®

Personal Assistant for Tracking Health

Pocket PATH **uses a smartphone custom app to assist recipients to manage health-related data and perform self-care behaviors.**



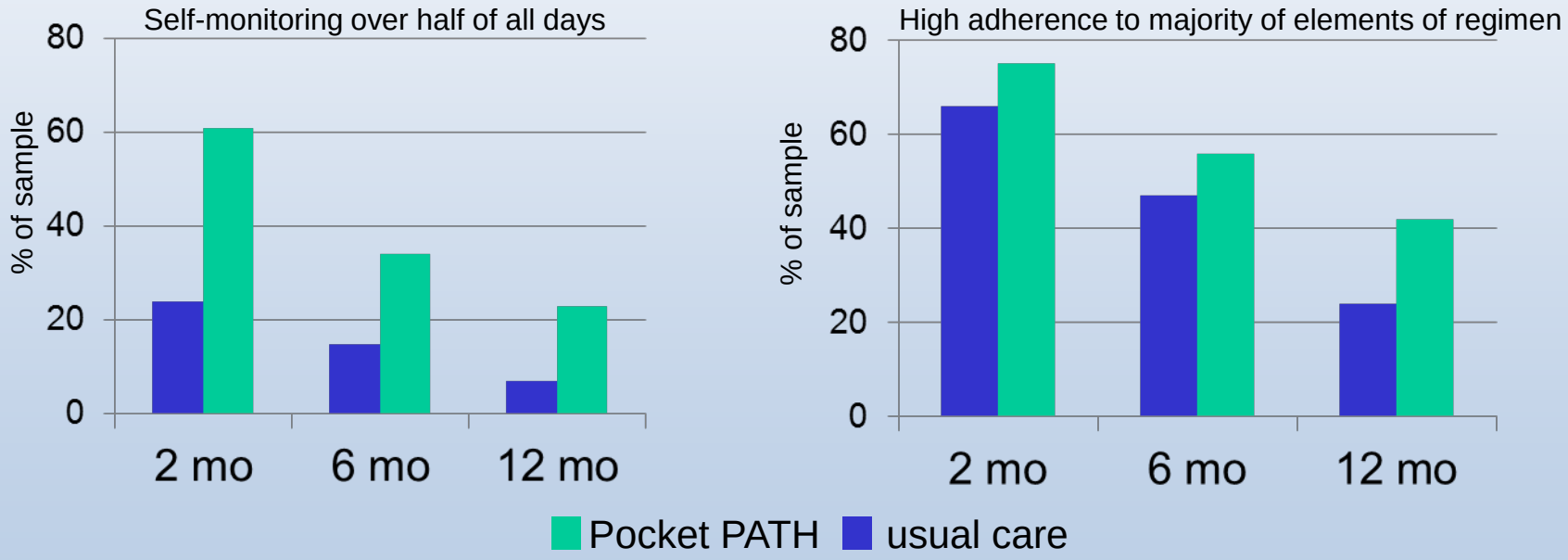




DeVito Dabbs et al., *Clin Transplant 2009; Am J Transplant*, 2016

Impact of 12-mo. Pocket PATH intervention

- n=201 randomized before hospital discharge posttransplant
- Intervention group (vs. usual care) had more frequent self-monitoring; higher regimen adherence; were more likely to report abnormal health indicators to the team
- No effects on rehospitalization or first year mortality



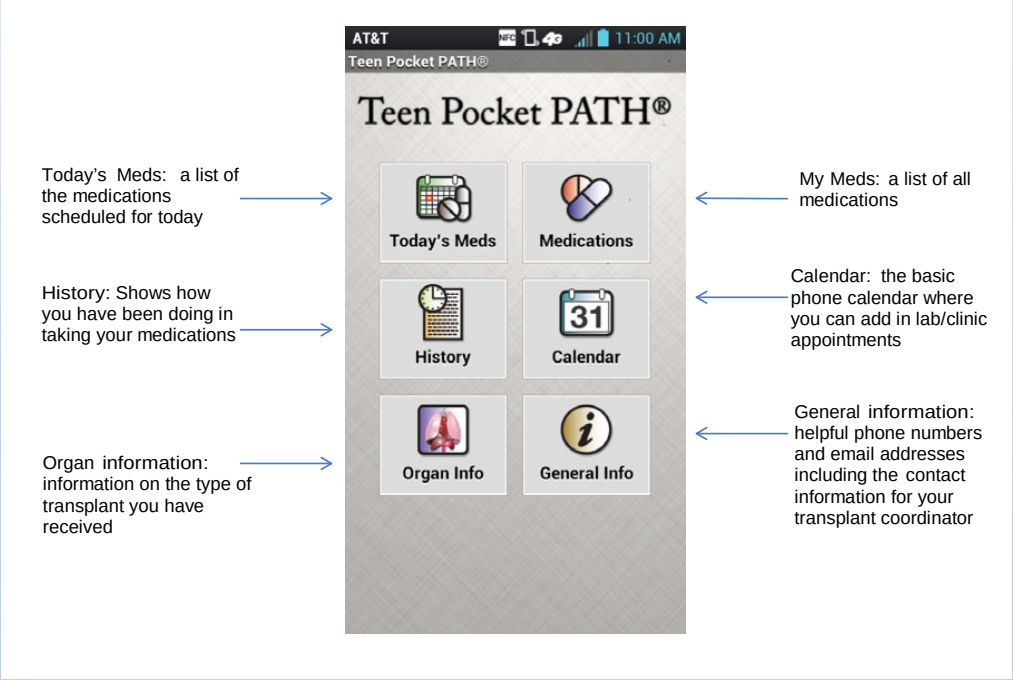
<u>Issues</u>: self-monitoring and adherence decreased over time in both groups; no followup after first year

DeVito Dabbs et al., *Am J Transplant*, 2016

Beyond the Pocket PATH trial

- Long-term follow-up of Pocket PATH Trial participants
  - behaviors affected in original trial appeared to contribute to reduced mortality risk in subsequent years *(Rosenberger et al., under review)*

- Extension to adolescent organ transplant recipients *(Shellmer et al., Pediatr Transplant 2016)*



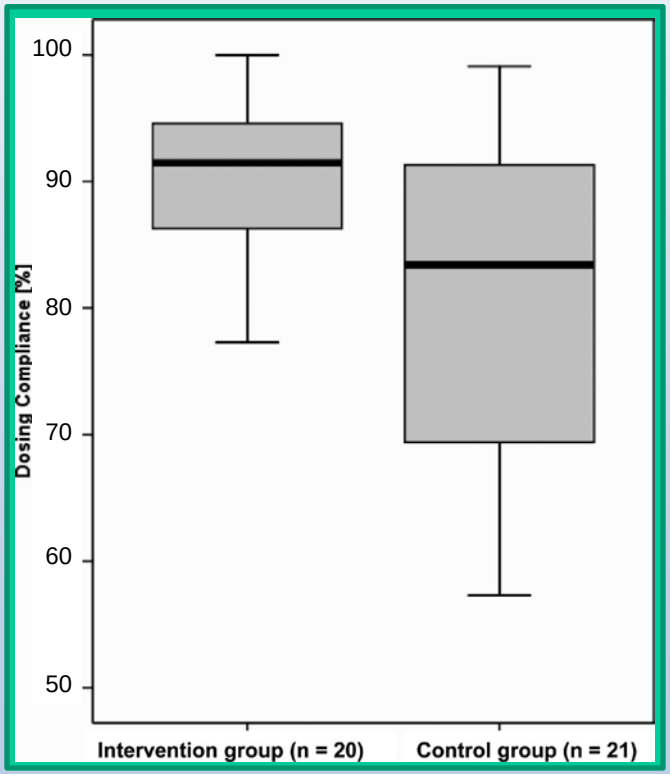
3. Face-to-face pharmacist-led education and monitoring interventions

- N=41 liver recipients, randomized controlled trial
- 12-month medication-focused intervention:
  - education before posttransplant hospital discharge
  - quarterly meetings with pharmacist to review meds, lab values, drug-related problems

Intervention group had:

- better medication dosing adherence (days with correct no. of electronic bottle openings)
- higher rates of target serum levels
- no effects on medication taking adherence (total bottle openings, electronic), self-reported adherence, graft rejections

Issues: small sample; no followup after first year



Klein et al., *Transplantation*, 2009

4. Face-to-face multicomponent psychoeducation & monitoring intervention

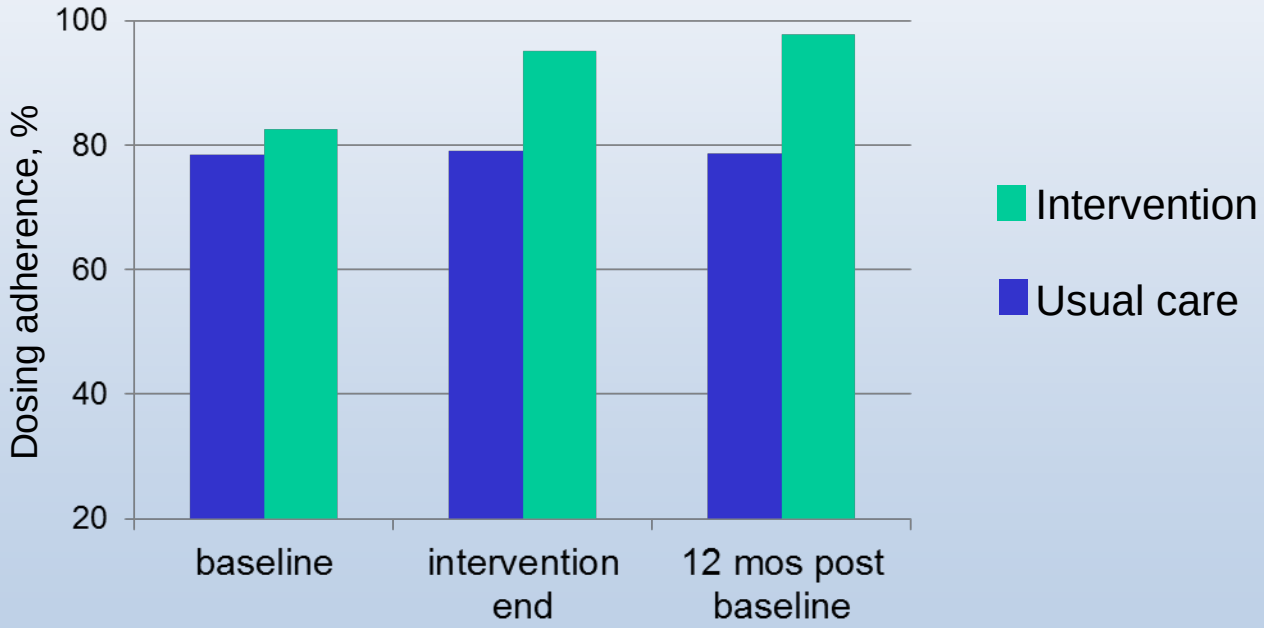
MAESTRO-Tx Study: Medication Adherence Enhancing STRategies in Solid Organ Tx

- N=205 recipients (heart, lung, or liver) > 1 year posttransplant, randomized controlled trial
- Intervention: medication-focused, bimonthly meetings for 6 mos
  - Electronic monitoring feedback and reminders; goal setting/action planning; education/social support; motivational interviewing
  - Tailoring of components based on patients' difficulties with adherence
- Adherence outcomes assessed at baseline, at end of intervention and 12 mos post-baseline
- Clinical event-free survival assessed over 5 years

Dobbels et al., *J Heart Lung Transplant, 2016, abstract*

Impact of 6-mo MAESTRO-Tx intervention

- Dosing adherence (days with /correct no. of bottle openings) and timing adherence (days when bottle opened at correct times) improved
- Clinical event-free survival showed promising but nonsignificant trend favoring intervention



<u>Issues</u>: complex intervention may not be feasible in standard practice; no follow-up on adherence beyond 12 months post-baseline

Dobbels et al., *J Heart Lung Transplant, 2016, abstract*

Conclusions: Adherence interventions in heart, lung or liver transplant

- Compared to ~15 studies in adult kidney transplant, very few studies to date
- Education alone is not effective (despite common beliefs in clinical practice)
- Multicomponent strategies can improve adherence
- Intervention tailoring for patient-specific difficulties may be critical
- Short follow-up periods in existing studies; durability and impact on clinical outcomes not clear

Outstanding issues

- What can transplant clinicians do today to help their patients? Could they use elements of interventions found to be effective?
- How to harness the combined power of mHealth and face-to-face interventions?
- Scalability of interventions:
  - Who can/should administer them?
  - Can/should transplant programs dedicate the needed resources?

Table 3. Strategies for Improving Adherence to a Medication Regimen.*

Identify poor adherence
- Look for markers of nonadherence: missed appointments ("no-shows"), lack of response to medication, missed refills
- Ask about barriers to adherence without being confrontational

Emphasize the value of the regimen and the effect of adherence

Elicit patient's feelings about his or her ability to follow the regimen, and if necessary, design supports to promote adherence

Provide simple, clear instructions and simplify the regimen as much as possible

Encourage the use of a medication-taking system

Listen to the patient, and customize the regimen in accordance with the patient's wishes

Obtain the help from family members, friends, and community services when needed

Reinforce desirable behavior and results when appropriate

Consider more "forgiving" medications when adherence appears unlikely†
- Medications with long half-lives
- Depot (extended-release) medications
- Transdermal medications

*from Osterberg & Blaschke, NEJM, 2005.

Pittsburgh at dusk

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Interventions to Improve Adherence Among Adult Renal Transplant Recipients

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American Journal of Transplantation 2013; 13: 2364–2373
Wiley Periodicals Inc.

doi: 10.1111/ajt.12341

Improving Outcomes of Renal Transplant Recipients With Behavioral Adherence Contracts: A Randomized Controlled Trial

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The objective of this randomized controlled trial was to assess the effects of a 1-year behavioral contract intervention on immunosuppressant therapy (IST) adherence and healthcare utilizations and costs among adult renal transplant recipients (RTRs). The sample included adult RTRs who were at least 1 year posttransplant, taking tacrolimus or cyclosporine and served by a specialty pharmacy. Pharmacy refill records were used to measure adherence and monthly questionnaires were used to measure healthcare utilizations. Direct medical costs were estimated using the 2009 Medicare Expenditure Panel Survey. Adherence was analyzed using the GLM procedure and the MIXED procedure of SAS. Rate ratios and 95% confidence intervals were estimated to quantify the rate of utilizing healthcare services relative to treatment assignment. One hundred fifty RTRs were enrolled in the study. Intervention group RTRs ($n = 76$) had higher adherence than control group RTRs ($n = 74$) over the study period ($p < 0.01$). And 76.1% of the intervention group compared with 42.7% of the control group was not hospitalized during the 1-year study period (RR = 1.785; 95% CI: 1.314, 2.425), resulting in cost savings. Thus, evidence supports using behavioral contracts as an effective adherence intervention that may improve healthcare outcomes and lower costs.

Key words: Behavior modification, healthcare costs, medication adherence, randomized controlled trial, renal transplant recipients

Abbreviations: ED, emergency department; IST, immunosuppressant therapy; MEPS, Medicare Expenditure Panel Survey; RCT, randomized controlled trial; RTR, renal transplant recipient.

Received 30 November 2012, revised 13 May 2013 and accepted 15 May 2013

Introduction

Following renal transplantation, immunosuppressant therapy (IST) adherence plays a critical role in maintaining graft function, yet the rate of IST nonadherence among renal transplant recipients (RTRs) is approximately 36% per year (1–3). IST nonadherence is considered the leading avoidable cause of graft failure, with odds of failure sevenfold greater in nonadherent RTRs compared to adherent RTRs (4). Given the negative consequences associated with IST nonadherence, healthcare professionals desire evidence-based interventions to facilitate and maintain adherence among RTRs, which in turn may contribute to improved outcomes and reduced healthcare utilizations and costs. However, a significant knowledge gap remains in the development and implementation of efficacious interventions to foster IST adherence.

A search of PubMed (years unlimited) revealed few published studies of interventions targeting IST adherence among adult RTRs (5–9). Existing studies are hampered by ineffective interventions and/or lack of examination of outcomes related to adherence such as healthcare utilizations and costs, which were found to be associated with decreased IST adherence levels in a retrospective cohort study by Pinsky et al. (2,6–9). Given the limits of prior published interventional studies, prospective research is needed to evaluate the effects of interventions on IST adherence and healthcare outcomes among adult RTRs.

Previous studies suggest biological, affective, cognitive, behavioral and environmental factors may impact health behaviors and act as causes of nonadherence (10–14). Such findings are consistent with the tenets of social cognitive theory, which postulates that behavior is influenced by environmental and personal (biological, affective and cognitive) factors and aspects of the behavior itself (15–17). Therefore, it would logically follow that interventions targeting a particular health behavior, such as adherence,

Background

- **<u>Behavioral contracting</u>: a behavior modification technique, grounded in social cognitive theory, in which a patient-specific, written agreement or contract is developed between an individual and healthcare professional**
  - The contract identifies a target behavior and those factors that influence the behavior, and proposes strategies to modify the target behavior to achieve a desired outcome

Chisholm-Burns MA, et al. Am J Transplant 2013;13:2364-2373.

Methods

- **Study included renal transplant recipients (RTRs) 21 years of age or older who:**
  - Were at least one year post-transplant
  - Were prescribed tacrolimus or cyclosporine
  - Obtained immunosuppressant therapy (IST) from Avella Specialty Pharmacy for at least one year prior to study enrollment and during study

- **Participants in the intervention group met with the study clinical pharmacist at:**
  - Baseline to negotiate and sign the behavioral contract
  - 3, 6, and 9 months to review the contract, discuss progress toward the goal (highest possible IST adherence), update the contract, and re-sign the contract for the next quarterly period
  - 12 months to terminate the contract

Chisholm-Burns MA, et al. Am J Transplant 2013;13:2364-2373.

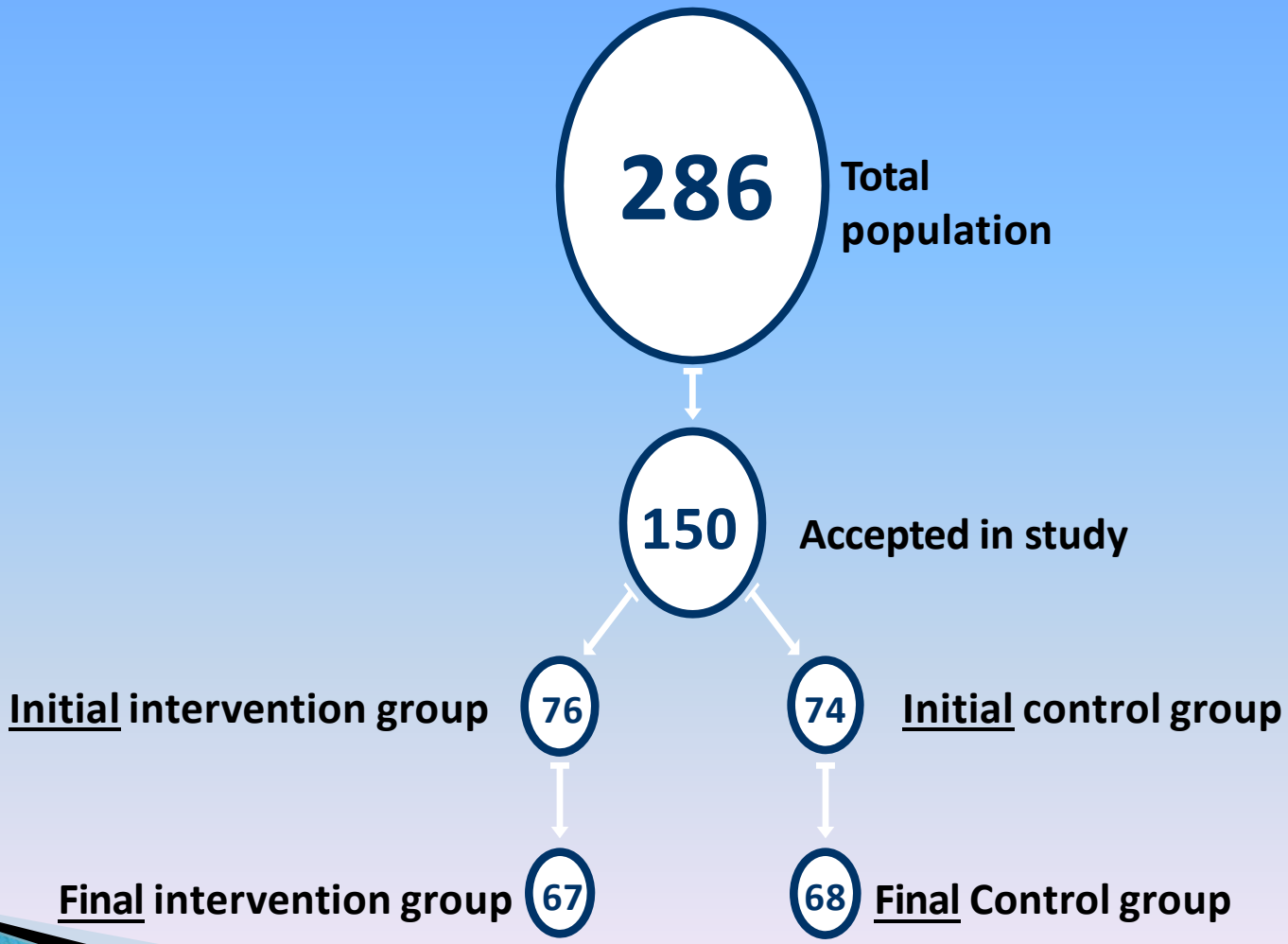
Methods

- **Behavioral contract addressed:**
  - Motivations for achieving IST adherence
  - Barriers that interfere with adherence
  - Solutions to barriers
  - Tools/strategies to remind RTR of dosing schedule
  - Possible consequences of non-adherence

- **Participants in the control group received standard (usual) care**

Chisholm-Burns MA, et al. Am J Transplant 2013;13:2364-2373.

Study Enrollment



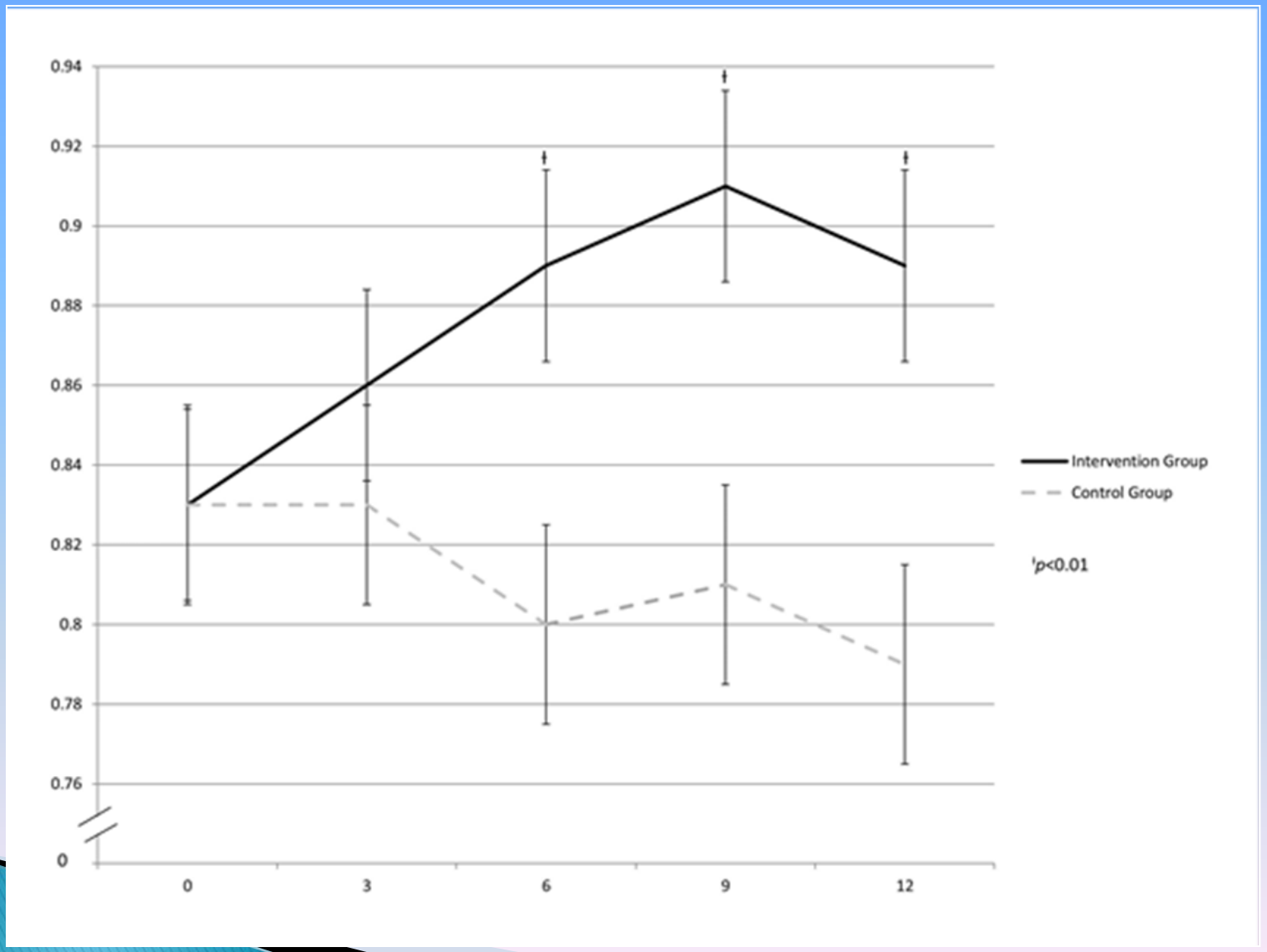
Chisholm-Burns MA, et al. Am J Transplant 2013;13:2364-2373.

Results

- No significant differences between intervention and control groups based on patient characteristics
- Baseline adherence was associated with months post-transplant (*rho* = -0.307, $p<0.001$), but no other patient characteristics
- The intervention group had significantly greater adherence compared to the control group at 6 months, 9 months, 12 months, and over the one-year study period ($p<0.01$)

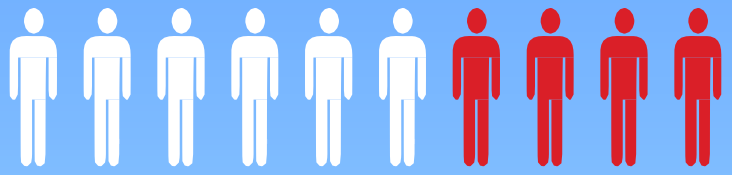
Chisholm-Burns MA, et al. Am J Transplant 2013;13:2364-2373.

IST Adherence Rates in Intervention Group Compared to Control Group

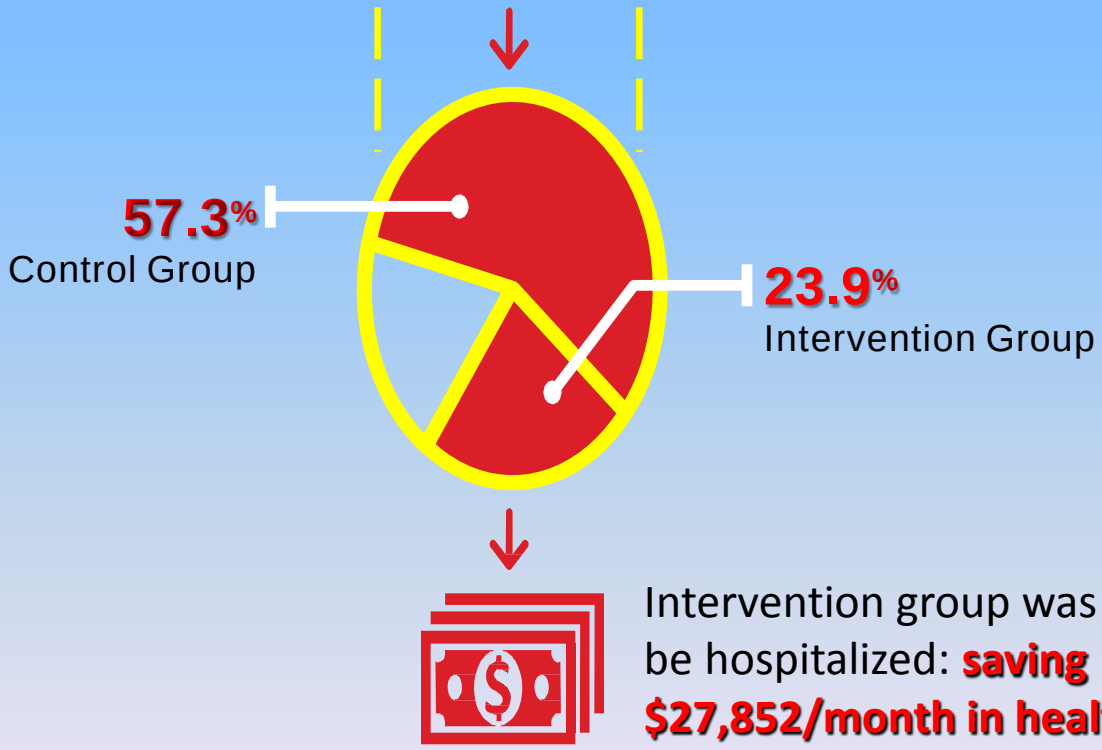


Chisholm-Burns MA, et al. Am J Transplant 2013;13:2364-2373.

Cost Analysis



40% of patients reported hospitalization during study



Intervention group was **78%** more likely not to be hospitalized: **saving $27,852/month in healthcare costs**

Chisholm-Burns MA, et al. Am J Transplant 2013;13:2364-2373.

Study Conclusions

- **Behavioral contracting is a practical and easy-to-employ adherence strategy that results in:**
  - Significant improvements in adherence
  - Decreased health care costs

Chisholm-Burns MA, et al. Am J Transplant 2013;13:2364-2373.

Clin Transplant 2001: 15: 330–336
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Impact of clinical pharmacy services on renal transplant patients' compliance with immunosuppressive medications

Chisholm MA, Mulloy LL, Jagadeesan M, DiPiro JT. Impact of clinical pharmacy services on renal transplant patients' compliance with immunosuppressive medications.
Clin Transplant 2001: 15: 330–336. © Munksgaard, 2001

Abstract: Background: Non-compliance with immunosuppressive medications may result in allograft rejection and is regarded as an important impediment to post-transplant care. This randomized, controlled trial evaluates the impact of clinical pharmacy services on renal transplant patients' compliance with immunosuppressive agents.
Methods: Patients who received a renal transplant at the Medical College of Georgia from February 1997 through January 1999 were randomized in the intervention or control group provided they met study criteria. In addition to routine clinic services at each clinic visit, patients in the intervention group received clinical pharmacy services, which included medication histories and review of patients' medications with an emphasis on optimizing medication therapy to achieve desired outcomes and minimizing adverse medication events. The clinical pharmacist also provided recommendations to the nephrologists with the goal of achieving desired outcomes. To promote medication compliance by using compliance enhancement strategies, the clinical pharmacist counseled patients concerning their medication therapy and instructed them how to properly take their medications. Patients in the control group received the same routine clinic services as the intervention group except that they did not have any clinical pharmacist interaction. Compliance rate (CR) was calculated and patient's compliance status was determined from the CR. The CR, the fraction of patients remaining compliant for each month, and the mean time patients were compliant were compared between groups. Whether there was a difference in the frequency of patients achieving 'target' immunosuppressive levels in the control and study groups was evaluated.
Results: The mean CR for patients who had clinical pharmacist intervention ($n = 12$) was statistically higher than the control group's ($n = 12$) mean CR ($p < 0.001$). During the 12-month post-transplant study period, patients in the intervention group had a longer duration of compliance than patients in the control group ($p < 0.05$). Additionally, patients who had clinical pharmacy services had a greater achievement of 'target' levels than patients who did not receive these services ($p < 0.05$).
Conclusions: Patients who received clinical pharmacy services with traditional patient care services had better compliance with immunosuppressants than patients who only received traditional patient care services. Results of this study suggest a multidisciplinary team that includes a clinical pharmacist as part of the care for post-transplant patients is beneficial for enhancing medication compliance.

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Key words: clinical services – immunosuppressant medications – kidney transplant – medication compliance

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Abbreviations: CR, compliance rate – MCG, Medical College of Georgia

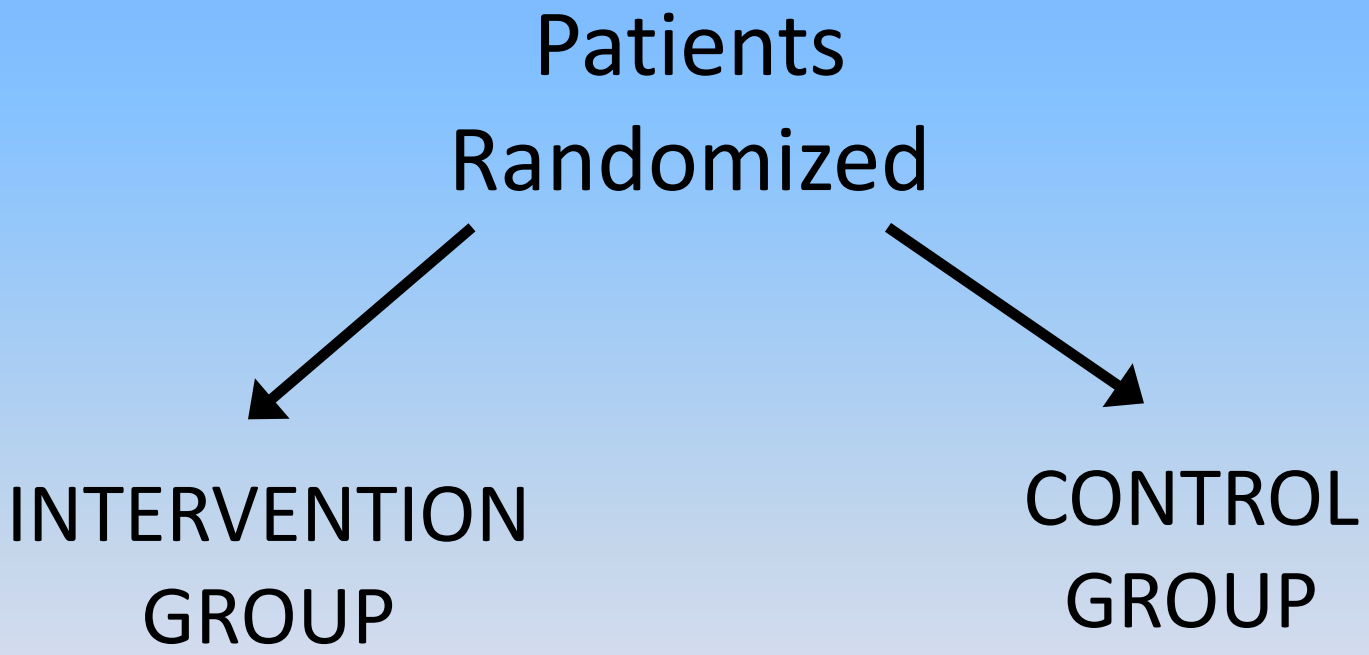
Impact of Clinical Pharmacy Services (CPS) on RTRs' Adherence to Immunosuppressant Medications

Study Inclusion Criteria

- Received a renal transplant (RT) at the Medical College of Georgia (MCG) from 02/97 – 01/99
- At least 18 years of age
- First RT
- No graft loss
- Received follow-up care at MCG for the first year post-transplantation
- Received IST from MCG Pharmacy

Chisholm MA, et al. Clin Transplant 2001;15:330-336.

Study Enrollment



Chisholm MA, et al. Clin Transplant 2001;15:330-336.

Methods

- **Study Groups**
  - Patients in the control group received traditional services — no clinical pharmacist (CP) intervention
  - Patients in the intervention group were seen by the CP at each clinic visit and interacted with the CP at least monthly

- **CP duties included**
  - performing medication reviews, with emphasis on preventing or resolving medication-related problems
  - monitoring therapy
  - providing medication recommendations and information
  - increasing patient access to medications
  - encouraging patient compliance to medications

Chisholm MA, et al. Clin Transplant 2001;15:330-336.

Results

Intervention

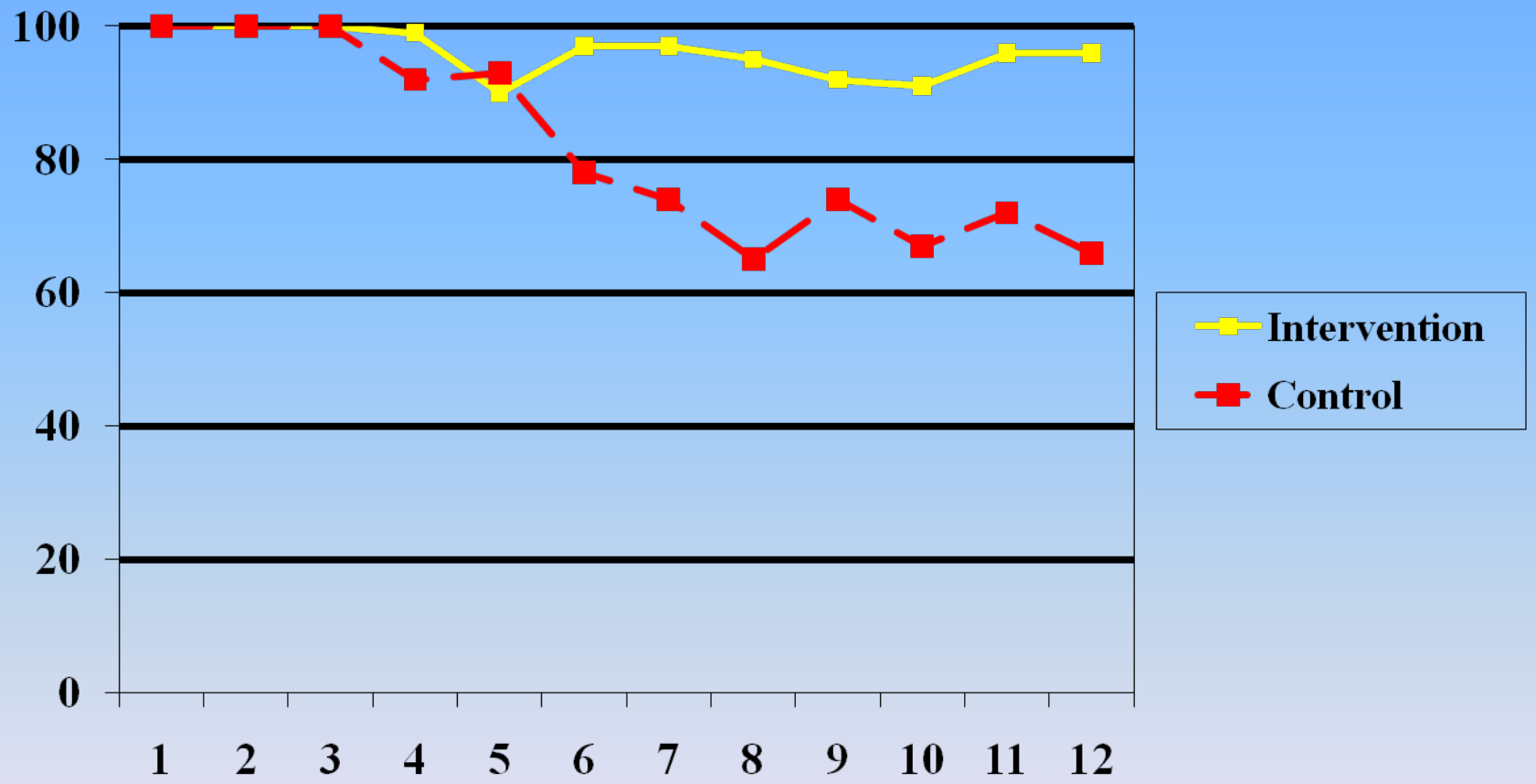
- 9 males (75%)
- 3 females (25%)
- Mean age = 50.1 ± 9.8
- 5 LRD (42%)
- 7 DD (58%)
- 7 Caucasians (58%)
- 4 African-Americans (33%)
- 1 Hispanic (9%)

Control

- 9 males (75%)
- 3 females (25%)
- Mean age = 49.7 ± 10.6
- 3 LRD (25%)
- 9 DD (75%)
- 7 Caucasians (58%)
- 5 African-Americans (42%)

Chisholm MA, et al. Clin Transplant 2001;15:330-336.

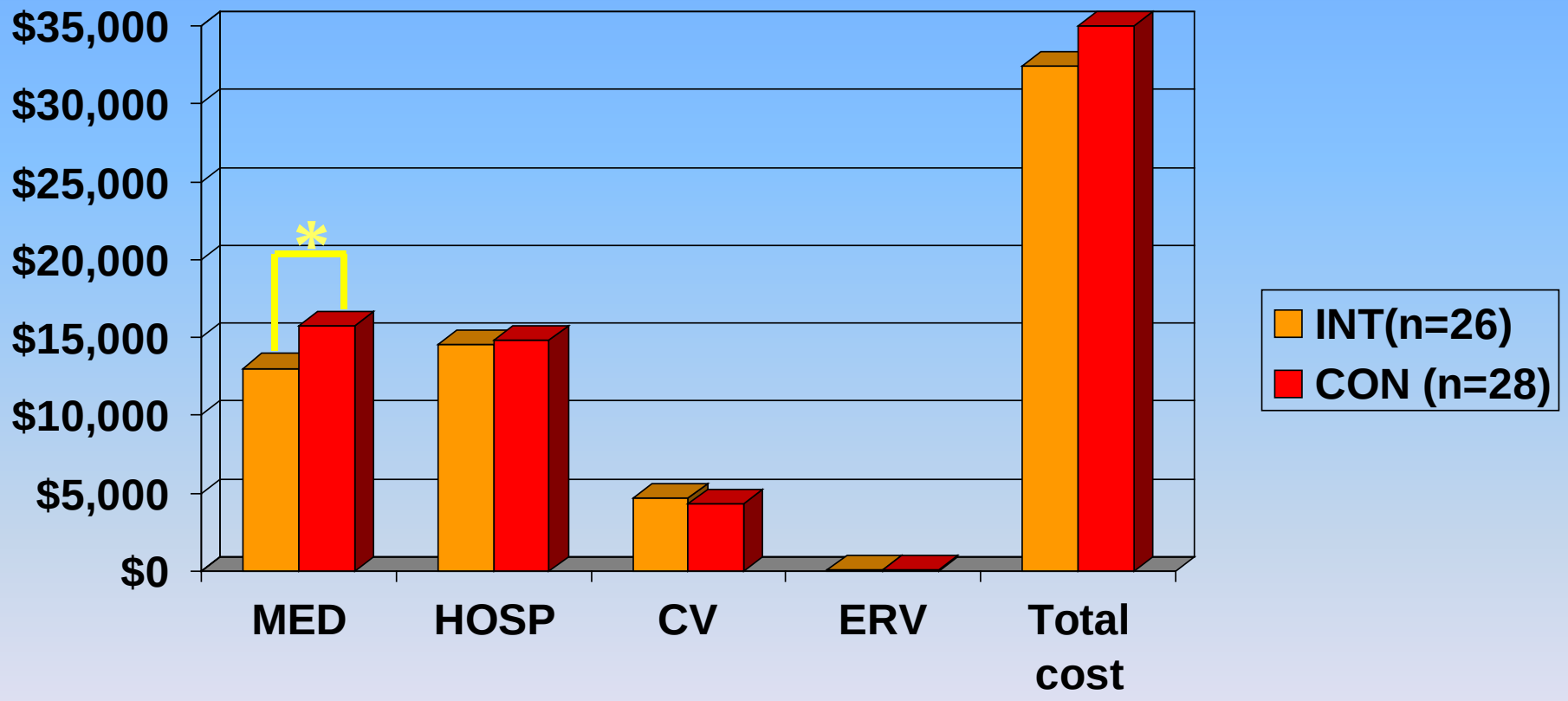
Results – Impact of CPS on IST Adherence



***p*<0.05**

Chisholm MA, et al. Clin Transplant 2001;15:330-336.

Results - Economic Evaluation



*p<0.05

Chisholm MA, et al. Clin Transplant 2001;15:330-336.

Results

- **Patients in the intervention group had a mean total cost/charge of $2,614 less per patient than patients in the control group**

Chisholm MA, et al. Clin Transplant 2001;15:330-336.

Results

- Patients in the intervention group had a mean total cost/charge of $2,614 less per patient than patients in the control group

- **This equals a total of $67,964 for the intervention patients**

Chisholm MA, et al. Clin Transplant 2001;15:330-336.

Summary

- Interventions have been developed that successfully improve IST adherence in transplant recipients
- Resources should be devoted to implementation of evidence-based interventions on a larger scale

Funding Sources

- NIDDK (1R01DK081347-01A2)
- Carlos and Marguerite Mason Trust

Interventions to Improve Medication Adherence and Outcomes in Adolescent Transplant Recipients.

Robert Ettenger MD

Distinguished Research Professor, Emeritus

Department of Pediatrics, Division of Nephrology

Note: Emphasized points are in RED

David Geffen School of Medicine

Mattel Children's Hospital UCLA

UCLA Children's Discovery and Innovation Institute

Designing Successful Interventions in Adolescent Transplant Recipients :
Some Questions and Challenges

What is a successful intervention?

- Measuring "taking adherence" vs. measuring absence of adverse biological outcomes

Different developmental stages, barriers and emotional problems require different approaches: One size doesn't fit all.

Inherent problems with adherence in adolescents

- Adolescents are concerned with the "here and now".
  - No pain due to missed medications
- Adolescents benefit from immediate feedback / incentives

Minimal Practical Guidelines on Which to Build Successful Adherence in Adolescent Medication in Transplantation (Ettenger & Stuber 2014)

Medical Team's Communication with Patient/Family

- Interactional Model rather than we/they approach
- Non-judgement- avoid selective attribution of blame
- Team Approach : Patient, Parents and Health Care Providers → Team
- Personal Chemistry : different healthcare providers for different patients

Post Transplant Interventions to Forestall Nonadherence

- Continual education with every visit
- On an individual basis, medication nonadherent behavior can fluctuate dramatically over time (Loiselle et al. Ped Trans 2015)
- Visits may need to be relatively more frequent to provide continual reinforcement ***even years after transplant***
- Written Instructions
- Address Patient and Parent Psychological and Social Problems Promptly

Designing Successful Interventions in Adolescent Transplant Recipients :
Classification of Interventions

- **Educational/Cognitive : Conveying information**
- **Counseling/Behavioral: Changing behavior to empower adolescents to participate in their care and develop new skill sets of self-care**
- **Psychological/Affective: Addressing feelings, emotions, and social relationships**
- **Mixed Interventions: Virtually all of the more recent interventions in the literature are multicomponent interventions.** (Pai and McGrady J Ped Psych 2014)
- **Immunobiological**
  - **Tolerance / Medication minimization: Adolescents should be considered for clinical trials**
  - **Improved Matching**
- **Medical**
  - **Simplifying Drug Regimen or Reducing Drug Burden**

Designing Successful Interventions in Adolescent Transplant Recipients:
Educational / Cognitive Interventions

An important part of every adherence intervention in adolescents (Salema et al J Adolesc Health. 2011)

Useful in interventions targeted towards patients and families with difficulty in transferring responsibility from parents to adolescents (Annunziato et al Ped Transpl 2008)

While patient and parent education is essential, *educational interventions alone are insufficient by themselves* to promote or sustain optimal adherence (Kahana et al J Ped Psychol 2008) (Dean et al. Arch Dis Child. 2010)

Adherence Interventions in Pediatric Patients with Chronic Disease
General Considerations (The Devil is in the Details)

Multicomponent interventions, especially those that use behavioral change as a component, appear to have the highest effectiveness with small to moderate effect sizes (Wu & Pai Pediatrics 2014) (Fredricks and Dore-Stites Curr Opin Organ Transpl 2010)

- **Education**
- **Parental involvement : Collaborative**
- **Self-monitoring**
- **Reinforcement**
- **Problem-solving**

IMB Model

Information

Motivation (Consider Incentives)

Behavioral Skills

+ Ameliorating Risk Factors and Barriers

Treatment effects are strongest immediately after intervention and dissipate over time. (Cortina et al. J Ped Psych 2013) (Pai and McGrady J Ped Psych 2014)

- **Successful interventions must focus on sustaining intervention effects**

Few RCTs in pediatric transplantation

Designing Successful Interventions in Adolescent Transplant Recipients:

Counselling/Behavioral : TAKE-IT (Foster et al BMC Nephrology 2014)

12 Month Multicenter Intervention RCT in 120 Adolescent Kidney Recipients

Study population patients meet with trained lay Coach every 3 months	• Interventions are Educational, Organizational, and Behavioral
Barriers identified by AMBS/PMBS; Coaches teach "Action-Focused Problem Solving"	• Problem Solving Skills • Concrete Contingency action plans for speccific occasions to develop appropriate habits
Medication Adherence monitored by	• Electronic Multi-dose Pillbox • Therapeutic Drug Level Variability Monitoring • Self-report • Biological Outcomes – e.g., biopsy proven rejection

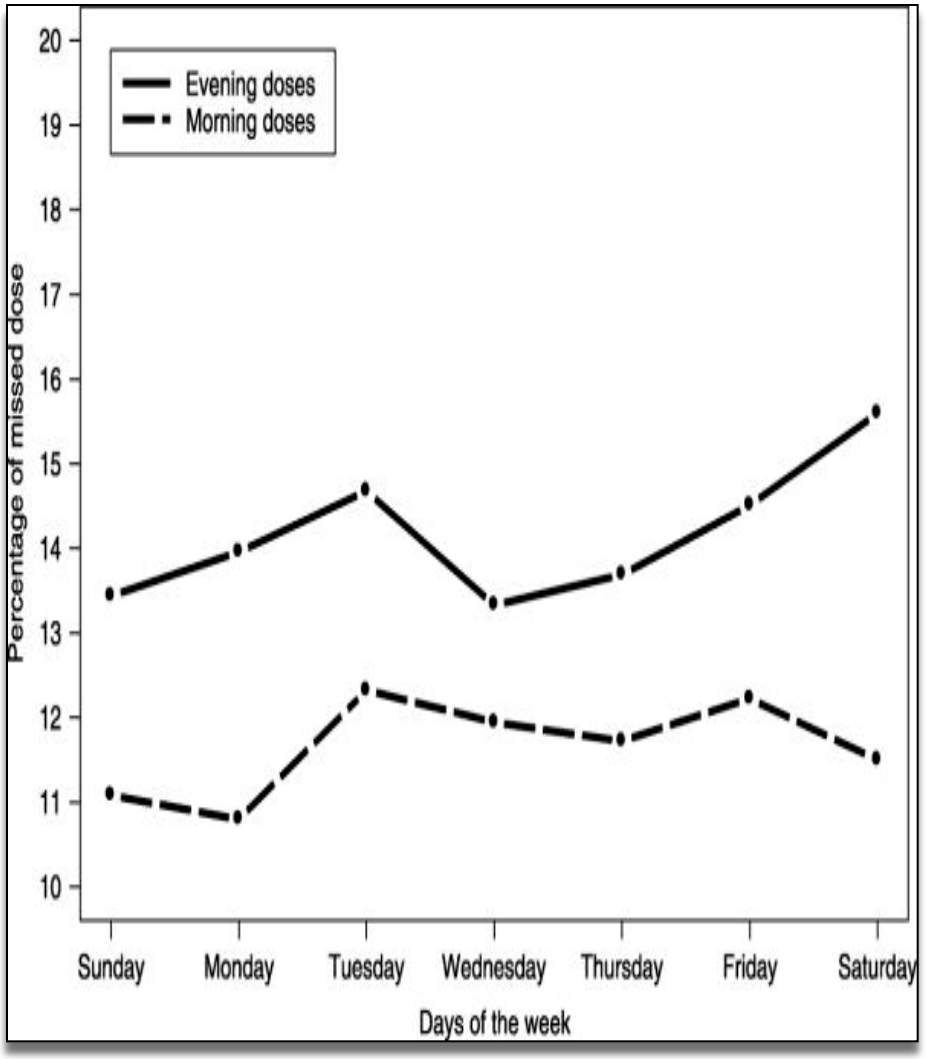
Designing Successful Interventions in Adolescent Transplant Recipients:

Post Traumatic Stress Disorder (PTSD)

(Shemesh et al Pediatr.2000:105:e29)

- Characterized by re-experiencing, avoidance and hyper arousal responses to previous traumas.
- Post-Traumatic Stress Disorder Reaction Index (PTSRI) administered in 19 patients.
  - 6 of 19 pediatric liver transplant recipients have + scores on all 3 components of PTSRI.
  - 3/6 with + PTSRI have documented nonadherence (P=0.02)
  - PTSD was treated in these 3 patients with good subsequent adherence
- At UCLA, parents of transplant patients have also been shown to experience PTSD (Young et al Pediatr 2003:6:e725)

Simplifying the Drug Regimen



Kuypers, Dirk; et al. Transplantation 2013

- **Poor adherence is significantly associated with increased medication frequency in pediatric CKD patients (Blytd-Hansen et al CJASN 2014)**
- **Consider and study more "forgiving" regimens**
  - **Hypothesis: A once daily regimen (e.g., Sirolimus + low dose once-daily Tacrolimus) or monthly Belatacept may be a regimen best suited for adolescents**
- **One danger – missing one dose means missing 24 hours of medication**

Designing Interventions in Adolescent Transplant Recipients: Transition: Pediatric-Centered to Adult-Centered Care

Transfer to adult-centered care is associated with worsening clinical outcomes (Watson Ped Neph 2000) (Prestige et al Ped Neph 2012)

- **Likely due to medication nonadherence (Shemesh et al Curr Opin Organ Transpl 2011)**
- **Conflicting single-center studies suggest poor outcomes are not universal (Akchurin et al Ped Transpl 2014) (Koshy et al Transplantation 2009)**

Transition needs to be developmentally, rather than age based

Transition tools exist to gauge readiness. (Ferris et al. Ren Fail 2012) (Gilleland et al J Ped Psychol 2012)

A single transplant transfer clinic between pediatric and adult programs can reduce mediication nonadherence (McQuillen et al. Can J Kid Health Dis. 2015)

Text Messaging / mHealth and Adolescent Adherence

Text Messaging in Adolescent Adherence with Chronic Disease : Pros and Cons (Wu and Hommel J Peds 2014)

- Pros
  - Convenience
  - Addresses forgetfulness
  - Possibility of instant feedback
- Cons
  - Costs
  - Intermittent cell service
  - Burnout

Text Messaging in Pediatric Liver Transplantation (Miloh et al Pediatrics 2009)

- Significant improvement in medication adherence and ↓rejection episodes
- 41% of patients dropped out of study
- Other studies in acne and SLE not as successful :
  - **Texts can be helpful but likely additional interventions are necessary**

Text Messaging / mHealth and Adolescent Adherence
Provocative New Developments

- **Headline: Texas hospital testing Proteus's ingestible sensor with pediatric organ transplant patients (Aug 26 2016)**

Remote Directly Observed Therapy

Has been beta tested successfully in adolescents with SS Anemia using computer platform (Creary et al. Ped Bl Cancer 2014)

Another Platform

Panel Discussion Session 2

1. How can we incentivize (or promote) adherence?
    a. Does one strategy work for all patients or is there a personalized way to incentivize adherence?
    b. Would electronic monitoring help? Would keeping track of e.g., tacrolimus or cyclosporine trough concentrations help?
2. What are some barriers to increasing transplant programmatic resources allocated to promoting adherence efforts?
3. How can transplant programs help patients to support each other in their efforts to adhere to their medical regimen after transplant?
4. What medication reminder systems are most acceptable and helpful to patients?
    a. What are the challenges to using them? How can we track the usefulness or success of these systems?
    b. How can we harness power of “gamification” (use of game design) and health apps to support patients’ ability to track their medication taking and other medical regimen requirements?
5. What is preventing the development of more “forgiving” drugs so it would be less critical if patients miss a dose?

U.S. FOOD & DRUG ADMINISTRATION

Open Public Comment Period

Meghana Chalasani
Office of Strategic Programs
Center for Drug Evaluation and Research
Food and Drug Administration

U.S. FOOD & DRUG ADMINISTRATION

Closing Remarks

Renata Albrecht, MD
Director, Division of Transplant and Ophthalmology Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration