Current considerations on factors that affect long-term graft survival

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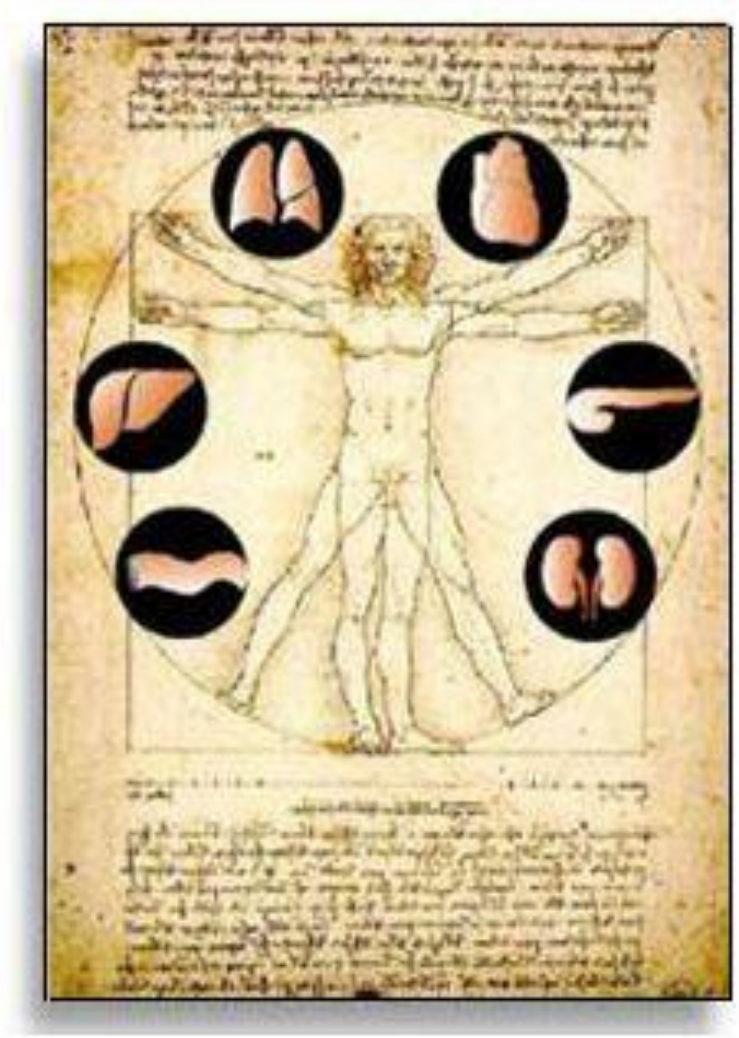
Presentation Aims

- History of transplantation
- Immunosuppressive Therapy
- Factors that affect long-term graft survival.
  - Variability if immunosuppressive medications in blood.
  - Non-adherence with recommended regimen.
  - Low levels of immunosuppressive medications in blood.

Organ Transplantation



Replacing failing organs is

The ultimate dream of medical care

and

A gift for life

First concepts of Organ Transplantation

200 AD

Hua-To from China replacing diseased organs with healthy ones.

First concept of organ transplantation for therapeutic purposes.

300 AD

Saints Cosmas & Damian carried out first transplantation of a leg in Italy

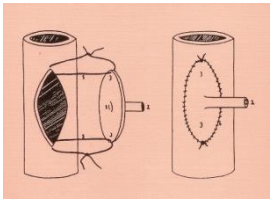
1597

Gaspare Tagliacozzi has transplanted skin from the patients own arm to reconstruct their syphilitic or diseased noses in Italy

Major 20th Century Advances in Transplantation

1901 **1905** **1944** **1954** **1963** **1965** **1967** **1969**

Anastomosis

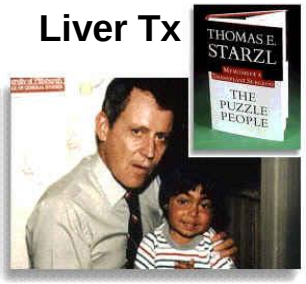


Carrel/Guthrie

Kidney Tx

Merrill / Murray

Liver Tx

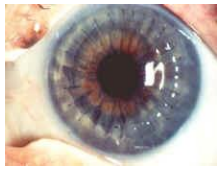


Tom Starzl

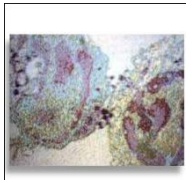
Heart Tx

Christiaan Barnard

Cornea Tx

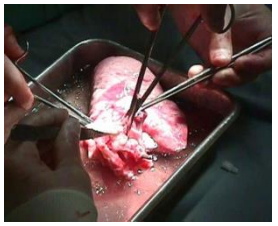


Eward Zirm

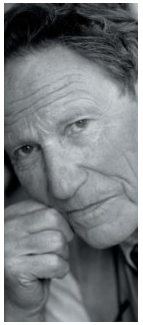


Peter Medawar
Rejection is an Immunological response

Lung Tx

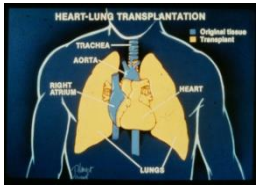


Fritz Derom



Jon van Rood
Organ Exchange based on the HLA-system
Eurotransplant Foundation

Heart/Lung Tx

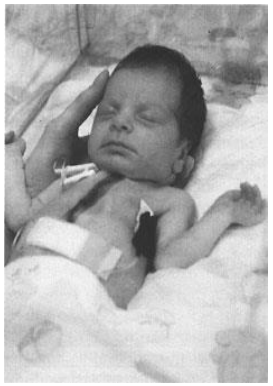


Denton Cooley

Major 20th Century Advances Transplantation

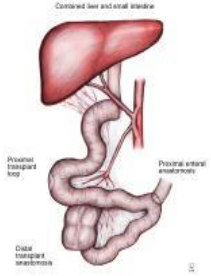
1983 **1991** **1998** **2004** **2005**

Xeno-Heart Tx



Baily

Intestine Tx

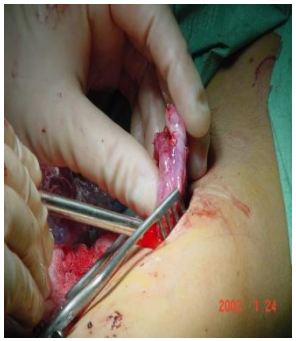


Tom Starzl

Hand Tx

Dubernard

Ovarium Tx



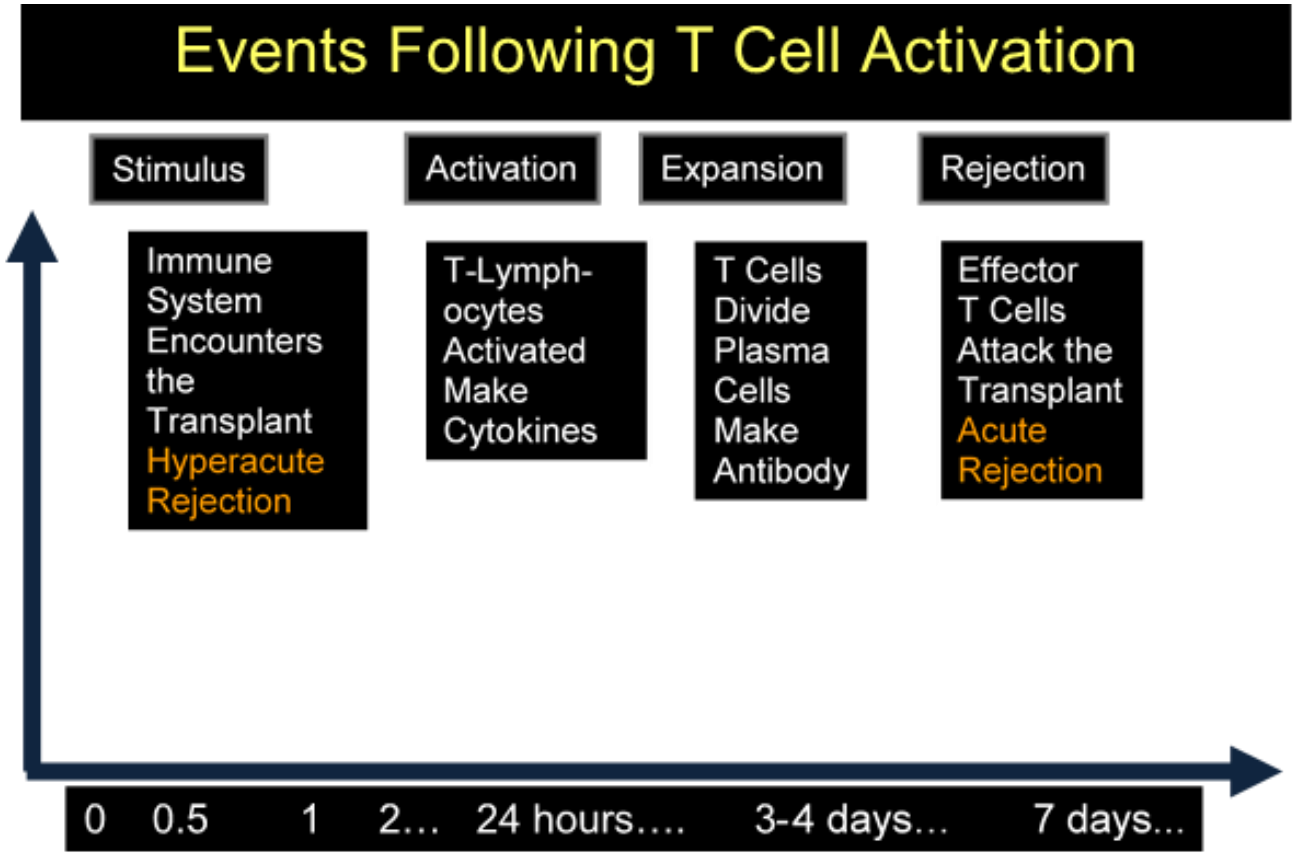
Hilders

Face Tx

What happens after transplantation?

IMMUNOLOGY

- The immune system recognizes graft from someone else as foreign and triggers **response** via ***immune cells*** *(e.g T-Lymphocytes)* or substances they produce - *cytokines* and ***antibodies***



What happens after transplantation

GRAFT REJECTION

- Rejection of transplanted organs is a bigger challenge than the technical expertise required to perform the surgery.

ACUTE REJECTION

- Usually occurs during the **first 6month**
- May be cell mediated (T-cell), antibody mediated or both

CHRONIC REJECTION

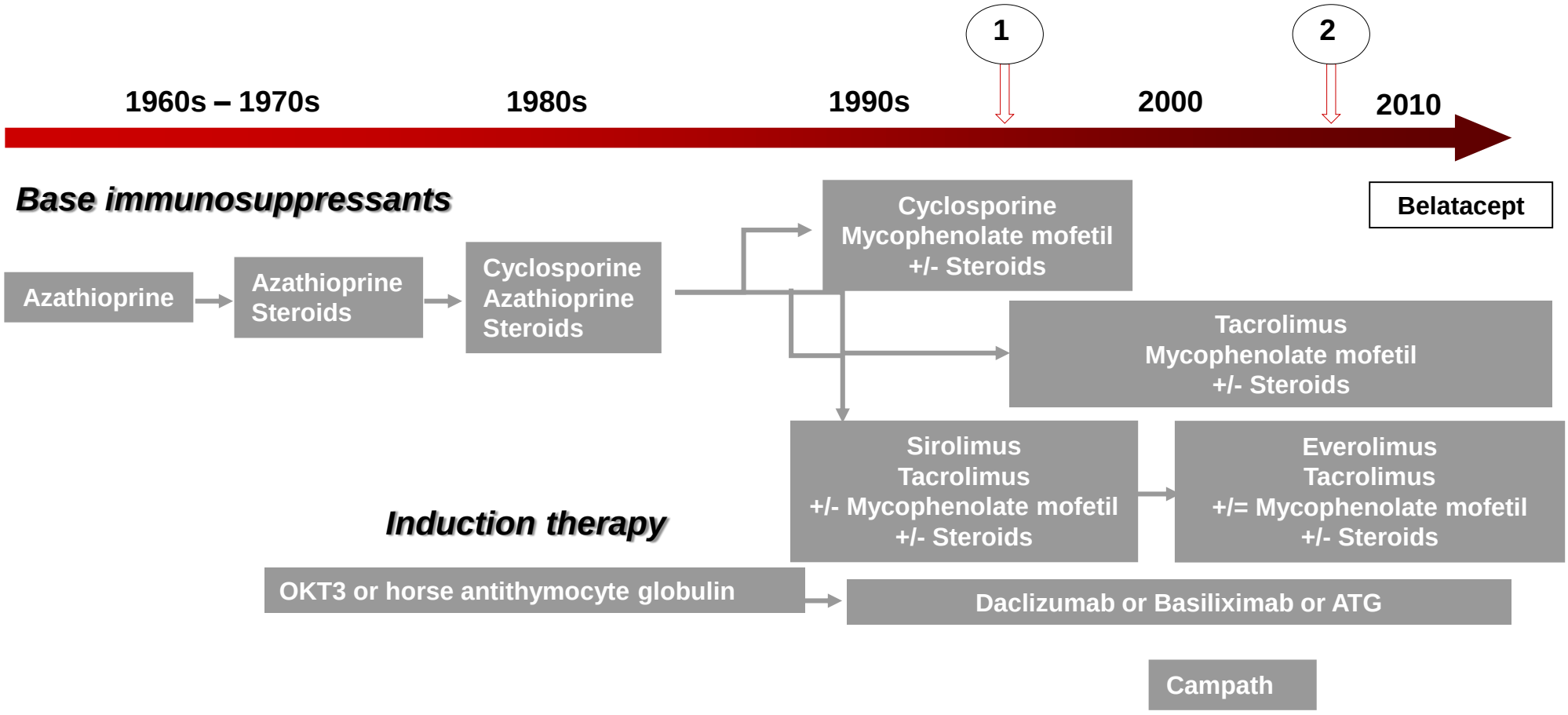
- **it occurs after 6month**
- ***Most common cause of graft failure***
- Antibodies play important role

IMMUNOSUPPRESSION

The principles of immunosuppression is ***maximize graft protection and minimize side effect***.

- The agents used to **prevent rejection** act predominantly on **T cells.**
- The need for immunosuppression is highest in the first 3 month but indefinite treatment is needed
- It increase the risk of infection and malignancy.

Development of Immunosuppressive Regimes

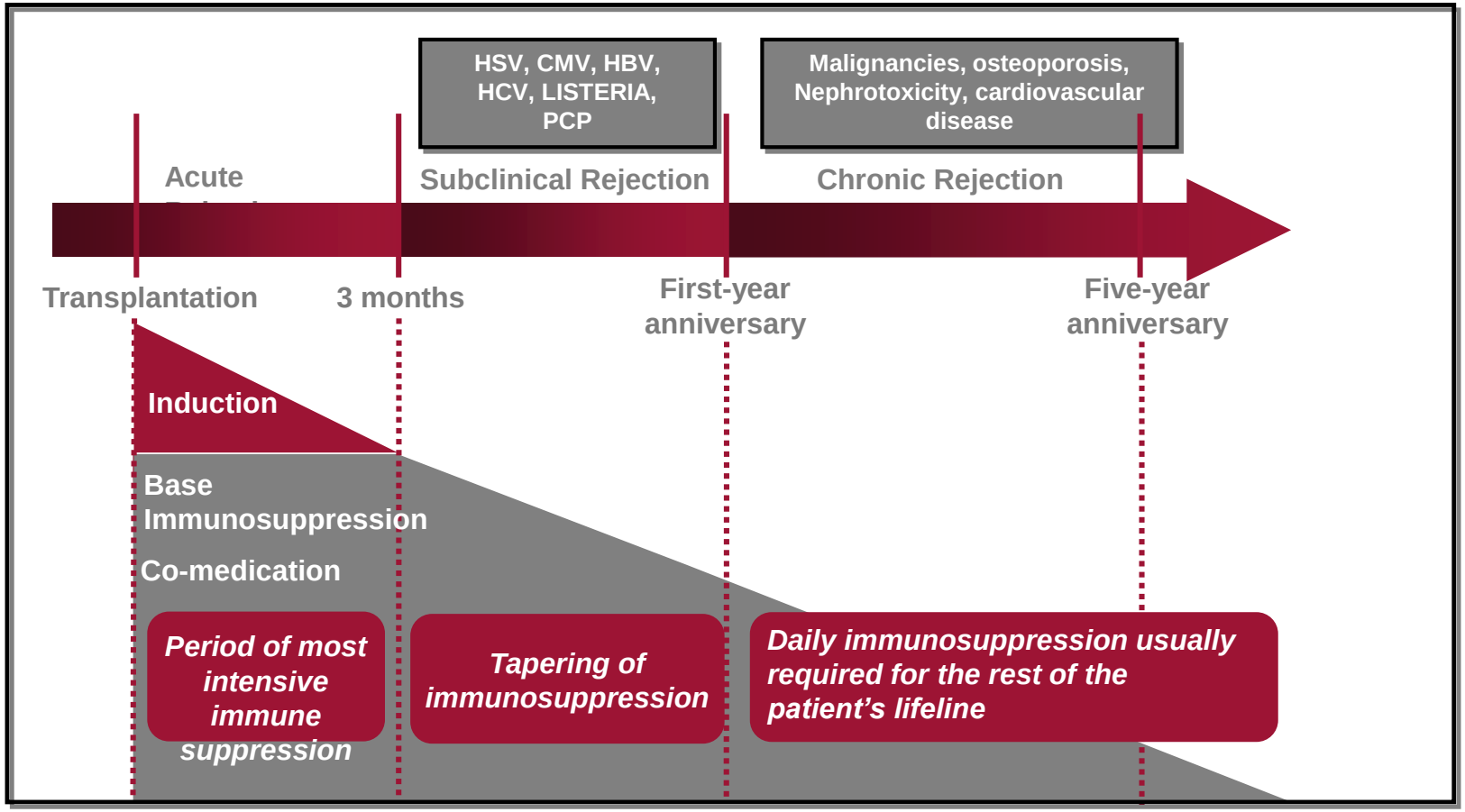


1: Cyclosporin microemulsion

2: Tacrolimus prolonged release

Source: Datamonitor

Post transplantation is generally characterised by three stages with varying degrees of immunosuppression need and use.



***HSV** = herpes simplex virus; **CMV** = cytomegalovirus; **HMV** = hepatitis B virus; **HCV** = hepatitis C virus*
***PCP** = Pneumocystis carinii pneumonia*

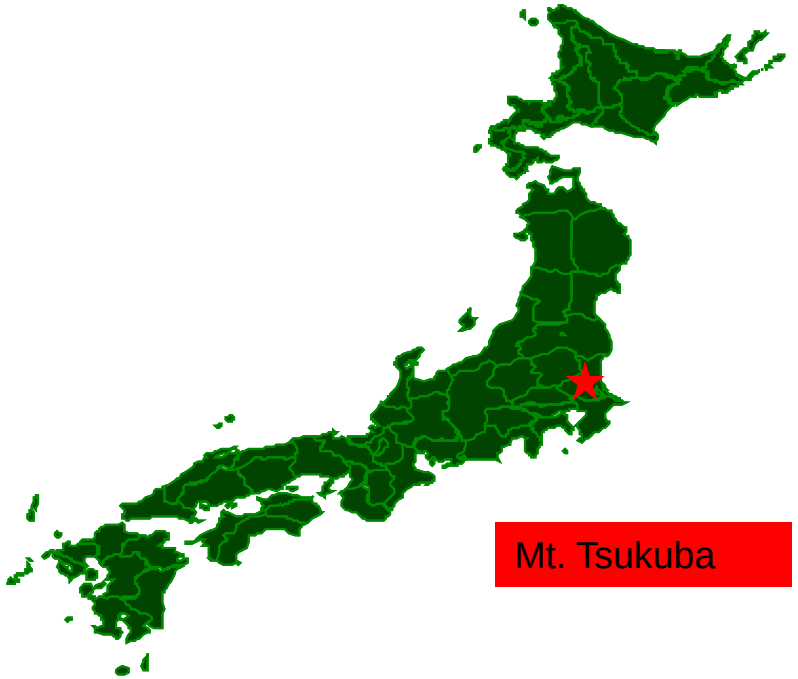
Discovery of cyclosporine and tacrolimus

1970

Cyclosporine was isolated from the fungus Tolypocladium inflatum from soil samples, Hardanger Vidda in Norway.

1984

Tacrolimus was isolated from actinomycete Streptomyces tsukubaensis from soil of Tsukuba City in Japan



Immunosuppression Consideration

- Tacrolimus and Cyclosporine are core components of immunosuppressive therapy.
- Both are usually combined with other immunosuppressive medications to form a dual or triple drug regimen
- Tacrolimus and Cyclosporine are recognised as a medications with narrow therapeutic index[1]
- Both exhibit large inter and intra-subject variability in pharmacokinetics (course of drug in the body).
- Therapy is optimsed on an individual patients basis using therapeutic drug monitoring (TDM) to adjust dosing.
- Concentrations at the end of dosing interval (C_{trough}) are used for TDM.

1. EMA/618604/2008 Rev. July 2010, EWP of the CHMP.

Factors that impact on the life of the transplanted kidney

- Intra-patient Variability of Tacrolimus and Cyclosporine exposure within an individual patient.
- Non-adherence with recommended regimen
- Over minimisation of Tacrolimus and Cyclosporine exposure

1. Lefaucheur C et al. *J Am Soc Nephrol* 2010;21:1398–1406; 2. Sellares J et al. *Am J Transplant* 2012;12:388–399; 3. Pascual M et al. *N Engl J Med* 2002;346:580–590; 4. Legendre C et al. *Transpl Int* 2014;27:19–27; 5. Sapir-Pichhadze et al, Kidney International, 2013

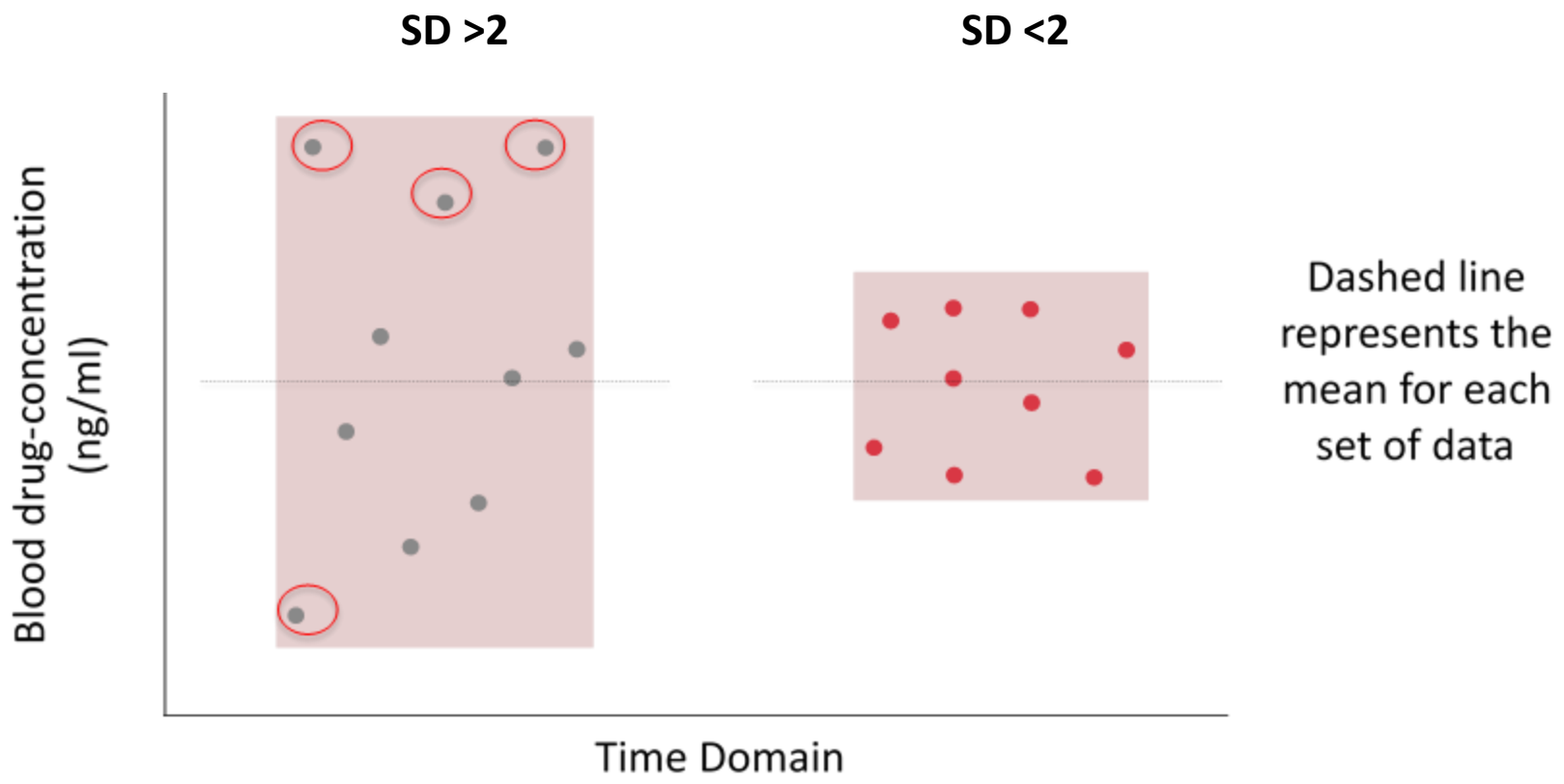
INTRA-PATIENT VARIABILITY AND GRAFT SURVIVAL

Definitions

Intra-patient variability	Tendency for the same dose of medication to provide different concentration in blood over time **within a single patient**
Standard deviation (SD)	▪ Measures spread of values around the mean ▪ Greater SD = higher variability
Coefficient of variation (CV)	▪ Ratio of the SD to the mean, expressed as a percentage ▪ CV(%) = SD/mean x 100 ▪ Greater CV = higher variability

Cervelli M, Russ G. Aus J Pharmacy 2012;93:83–6.

Defining intra-patient variability – an illustrative example



SD, standard deviation

Many factors can influence inter and intra-patient variability of cyclosporine and tacrolimus exposure

- Genetic polymorphisms (e.g., CYP3A5)[3]
- Drug-drug interactions[1]
- Non-adherence[4]
- GI motility[1]
- Diarrhoea[1]
- Food and drug interactions[1]
- Haematocrit[5,6]
- Plasma protein levels[5]
- Time post-transplant[1]
- Drug formulation[7]

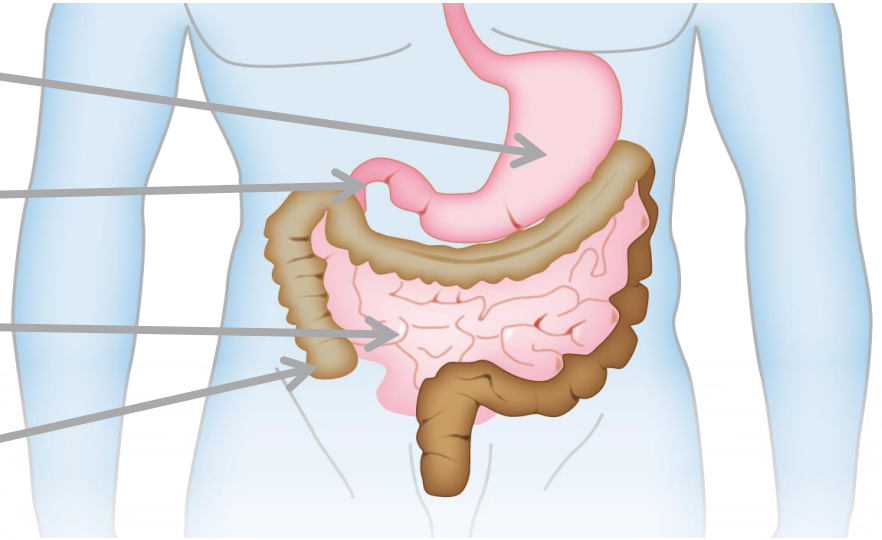
CYP3A, cytochrome P450-3A; GI, gastrointestinal

1. Shuker N, et al. Transplant Rev 2015;29(2):78–84. 2. Venkataramanan R, et al. Clin Pharmacokinet 1995;29:404–30. 3. Pashaee N, et al. Ther Drug Monit 2011;33(3):369–71. 4. Cervelli M, Russ G. Aus J Pharmacy 2012;93:83–6. 5. Advagraf summary of product characteristics. 6. Undre NA. Nephrol Dial Transplant 2003;18(Suppl1):i12–i15. 7. Stifft F, et al. Transplantation 2014;97(7):775–80

Oral cyclosporine and tacrolimus are pre-systemically metabolized in the GI tract cytochrome enzymes - CYP3A4/5

CYP3A4/5

- Stomach
- Proximal small bowel
- Distal small bowel
- Colon



CYP3A, cytochrome P450-3A; GI, gastrointestinal

1. Mekki Q, et al. Clin Pharmacol Ther 1993;53:238. 2. Prograf summary of product characteristics. 3. Jeong H, Chiou WL. Xenobiotica 2006;36(1):1–13. 4. Tuteja S, et al. Transplantation 2001;71(9):1303–7. 5. Cervelli M, Russ G. Aus J Pharmacy 2012;93:83–6

Genetic polymorphisms in the CYP3A5 gene cause variability in systemic exposure to tacrolimus

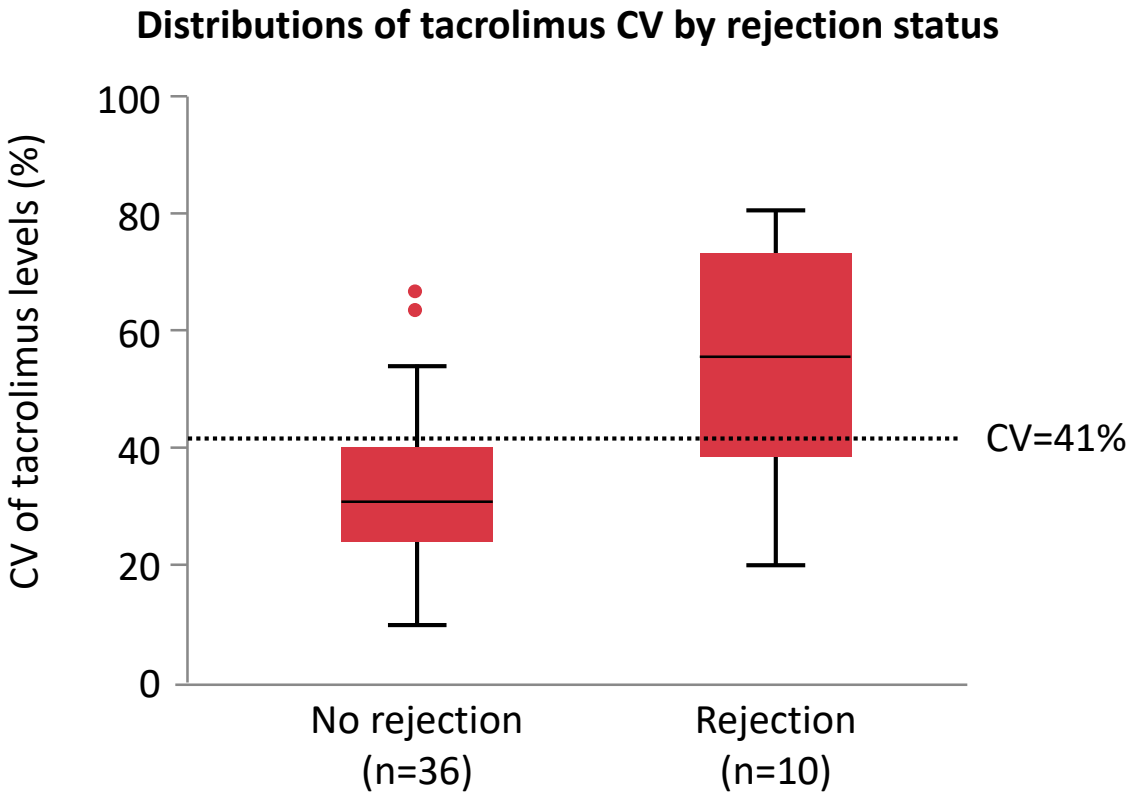
- Carriers of the CYP3A5*1 allele produce functional CYP3A5 protein[1]
  - Fast metabolisers of cyclosporine and tacrolimus[1]
  - Higher prevalence of CYP3A5*1 allele in specific populations black patients[1]

- Homozygous carriers of the CYP3A5*3 allele produce low/undetectable levels of CYP3A5 protein[1]
  - Slow metabolisers of cyclosporine and tacrolimus[1]

CYP3A, cytochrome P450-3A; GI, gastrointestinal

1. Staatz CE, et al. Clin Pharmacokinet 2010;49(3):141–75. 2. Hesselink DA, et al. Clin Pharmacokinet; 2014;53(2):123–39. 3. Elens L, et al. Clin Chem 2011;57(11):1574–83

High intra-patient variability correlates with increased risk of rejection in paediatric kidney allograft recipients



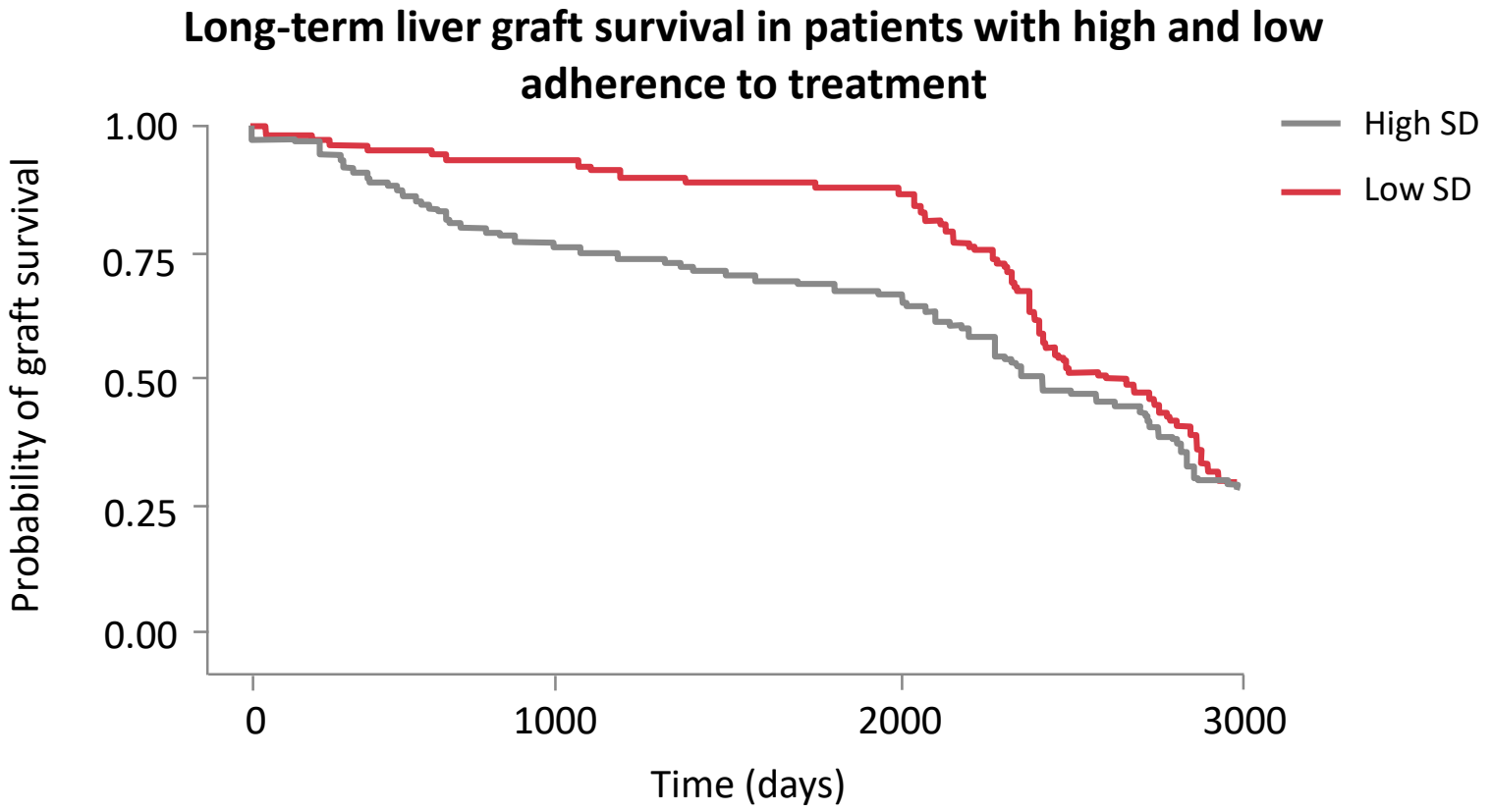
- Median tacrolimus CV was higher in patients with biopsy-proven rejection than in those without rejection (53.4% vs. 30.0%, p=0.005)

Tacrolimus CV >41% was associated with an increased risk of allograft rejection (OR 9.7, p=0.005)

CV, coefficient of variation; OR, odds ratio

Adapted from Hsiau M, et al. Transplantation 2011;92(8):918–22

High intra-patient variability in tacrolimus exposure early post-transplant is associated with an increased risk of liver graft failure



Variability during the 6–18 month post-transplant period was independently associated with graft failure (HR 1.005 per unit increase in SD, p=0.04)

HR, hazard ratio; SD, standard deviation

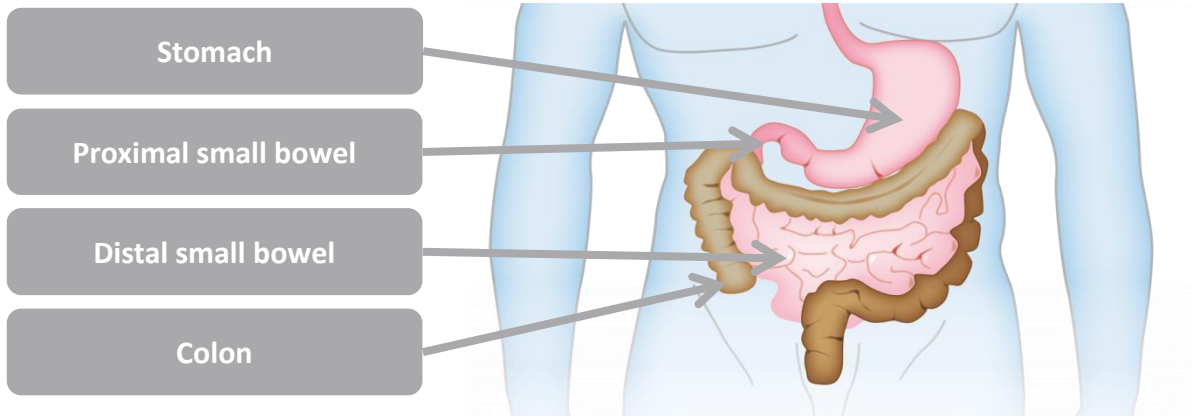
Adapted from Lieber S, et al. Dig Dis Sci 2013;58(3):824–34

Alterations in formulations can decrease variability by delivering the drug before or after proximal small bowel.

Cyclosporine micro-emulsion[1]

Prolonged release tacrolimus formu;ations[2]

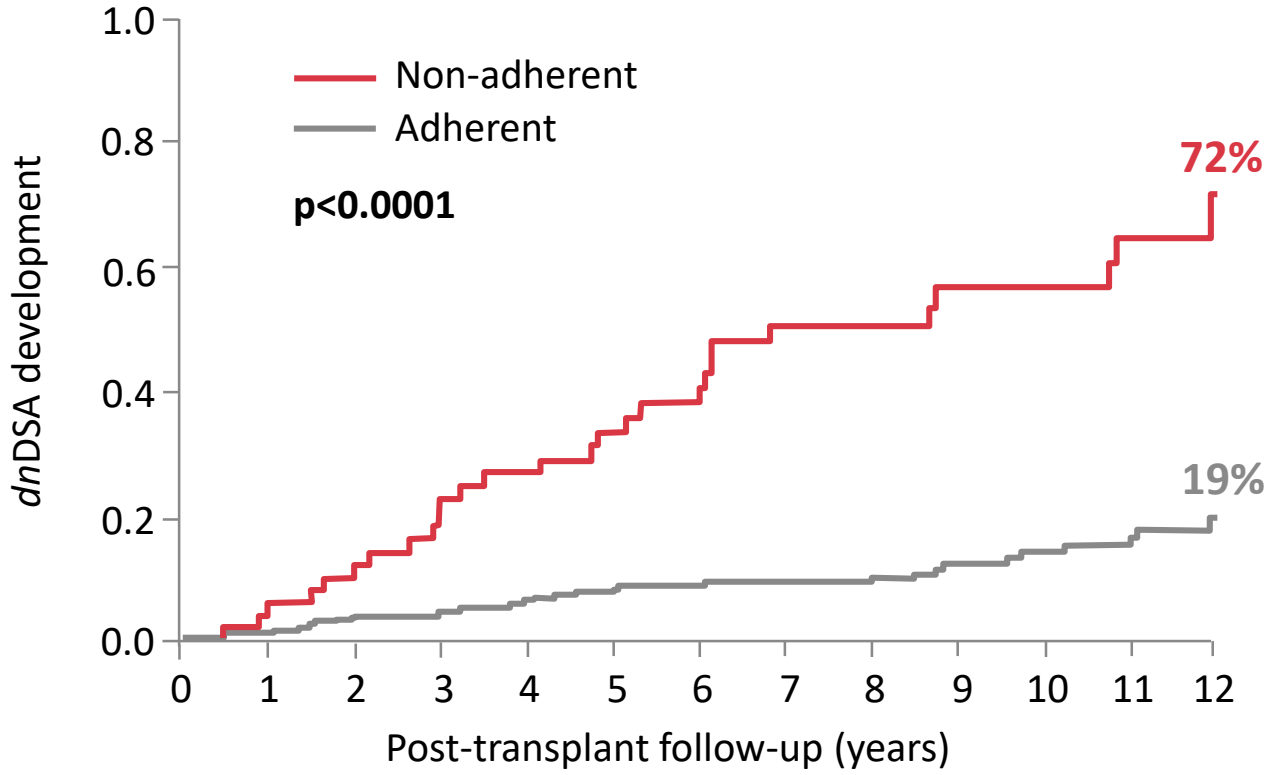
CYP3A4/5*



1. Kahan et al, Transplantation 1995; 2 Stifft F et al. Transplantation 2014;97: 775-780

Non-adherence and long-term outcomes

Non-adherence is a predictor of *dn*DSA development in kidney transplantation

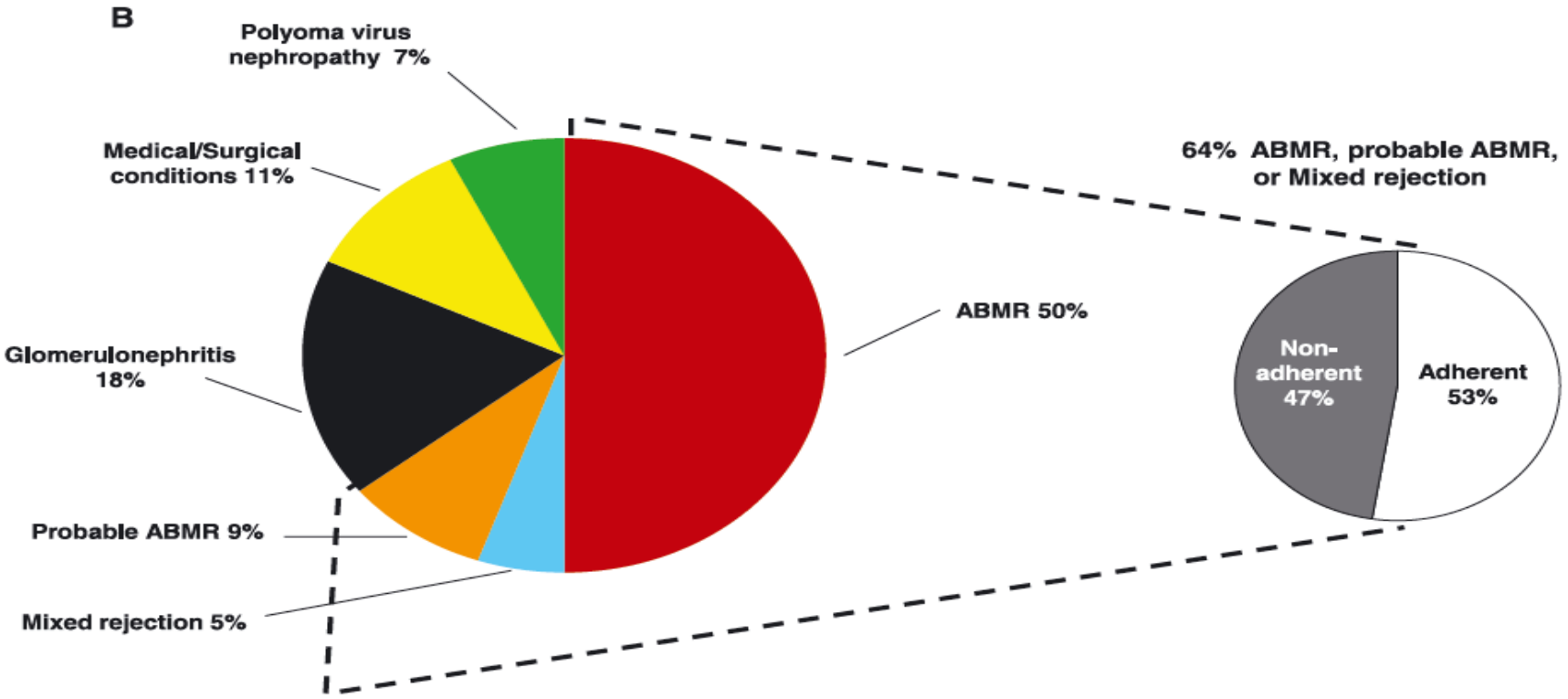


Non-adherence was an independent predictor of allograft failure following identification of *dn*DSA (HR 5.51, p<0.0001)

DSA, *de novo* donor-specific antibody; HR, hazard ratio

Adapted from Wiebe C, et al. Am J Transplant 2015;15(11):2921–30

Attributed causes of graft failure



Sellarés J et al. *Am J Transplant* 2012;12;388–399.

Non-adherence – a definition


Meeting Report

Nonadherence Consensus Conference Summary Report

"Deviation from the prescribed medication regimen..."[1]

CLINICAL[2]

Resulting in clinically-measureable events (e.g., acute rejection)

SUBCLINICAL[2]

Without resulting in clinically-measureable events

1. Fine RN, et al. Am J Transplant 2009;9(1):35–41. 2. Laederach-Hofmann K, Bunzel B. Gen Hosp Psychiatry 000;22(6):412–24

Features of non-adherence

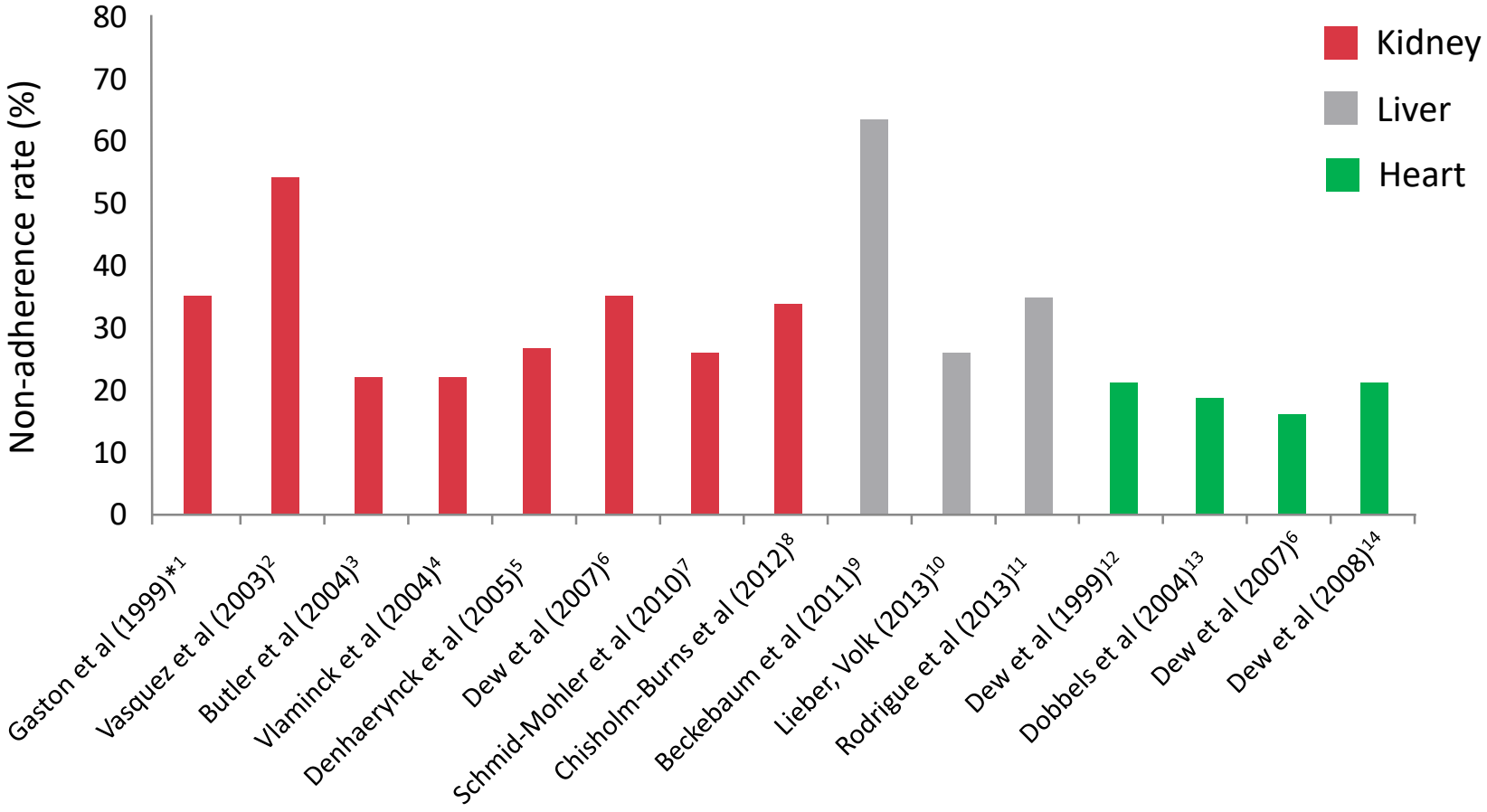
Non-adherence can be...

- At any point post-transplant (tends to increase with time)[1]
- Missing the occasional dose[2,3]
- Missing successive doses (taking a drug holiday)[2,3]
- Not taking the right dose[2]
- Not taking the medicine at the correct time[2,3]
- Taking the medicine inappropriately (e.g., with/without food)[4]

Due to the complexity of their therapeutic regimens, transplant recipients are particularly prone to medication non-adherence[5]

1. Kidney Disease: Improving Global Outcomes (KDIGO) Transplant Work Group. KDIGO clinical practice guideline for the care of kidney transplant recipients. Am J Transplant 2009;9(Suppl 3):S1–S157. 2. O'Carroll RE, et al. Liver Transpl 2006;12(12):1862−8. 3. Schmid-Mohler G, et al. Clin Transplant 2010;24(2):213−22. 4. Advagraf summary of product characteristics. 5. Laederach-Hofmann K, Bunzel B. Gen Hosp Psychiatry 2000;22(6):412–24

Non-adherence rates are significant and likely underestimated in solid organ transplantation



*Included only non-adherence associated with graft loss beyond 6 months post-transplant

1. Gaston RS, et al. Transplant Proc 1999;31(4A):21S−23S. 2. Vasquez EM, et al. Am J Health Syst Pharm 2003;60(3):266−9. 3. Butler JA, et al. Transplantation 2004;77(5):769−76. 4. Vlaminck H, et al. Am J Transplant 2004;4(9):1509−13. 5. Denhaerynck K, et al. Transpl Int 2005;18(10):1121−33. 6. Dew MA, et al. Transplantation 2007;83(7):858−73. 7. Schmid-Mohler G, et al. Clin Transplant 2010;24(2):213−22. 8. Chisholm-Burns M, et al. Clin Transplant 2012;26(5):706−13. 9. Beckebaum S, et al. Transpl Int 2011;24(7):666–75. 10. Lieber SR, Volk ML. Dig Dis Sci 2013;58(3):824–34. 11. Rodrigue JR, et al. Prog Transplant 2013;23(4):319–28. 12. Dew MA, et al. J Heart Lung Transplant 1999;18(6):549–62. 13. Dobbels F, et al. J Heart Lung Transplant 2004;23(11):1245–51. 14. Dew MA et al. Transplantation 2008;85(2):193–202

Measuring non-adherence

Assessment tools for non-adherence[1]

- Self-reporting by patient
- Reporting by friends and family
- Patient diaries
- Questionnaires (e.g., BAASIS© Interview Questionnaire)
- Laboratory tests (drug levels)
- Medical record review, clinical outcomes
- Prescription refills
- Monitored pill counts
- Electronic monitoring devices

It is difficult to accurately measure medication non-adherence[2]

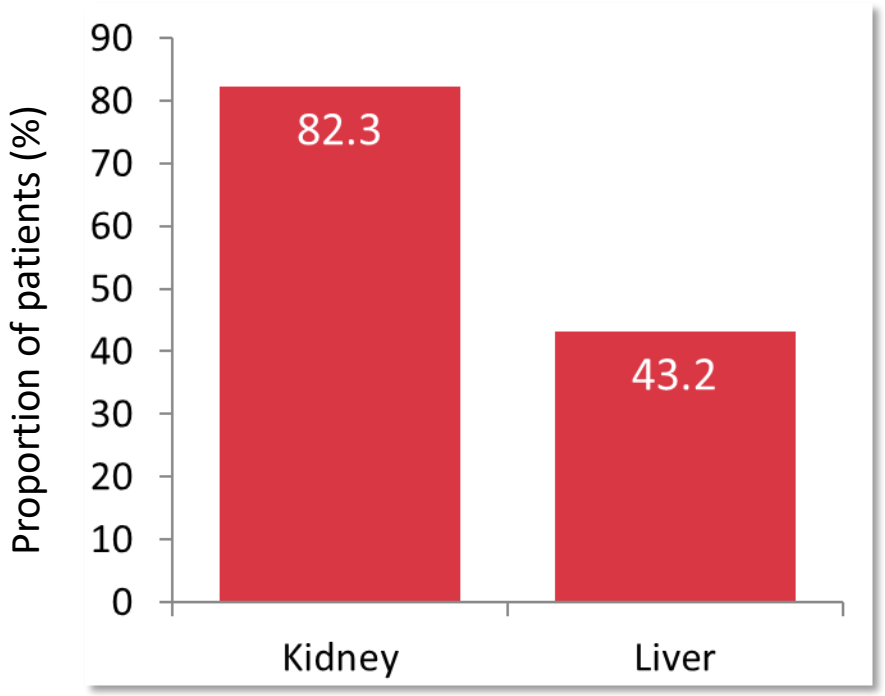
Table adapted from Morrissey PE, et al. (2007)

1. Morrissey PE, et al. Drugs 2007;67(10):1463–81. 2. Kidney Disease: Improving Global Outcomes (KDIGO) Transplant Work Group. KDIGO clinical practice guideline for the care of kidney transplant recipients. Am J Transplant 2009;9(Suppl 3):S1–S157

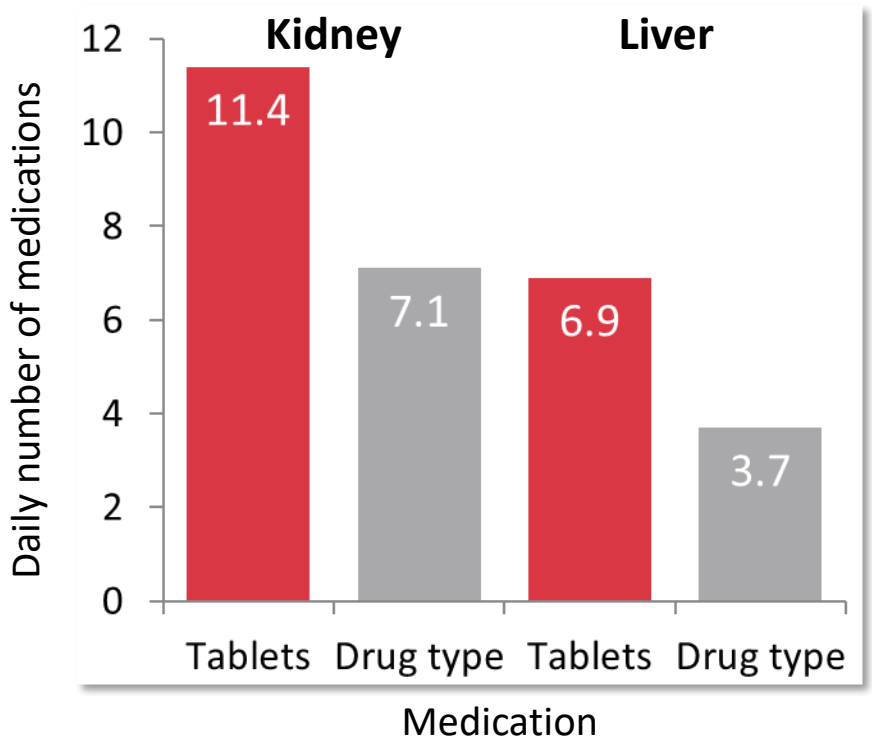
PATIENT DOSING PATTERNS AND PREFERENCES

Kidney and liver transplant patients often have high treatment burden

Proportion of transplant patients taking ≥2 immunosuppressants



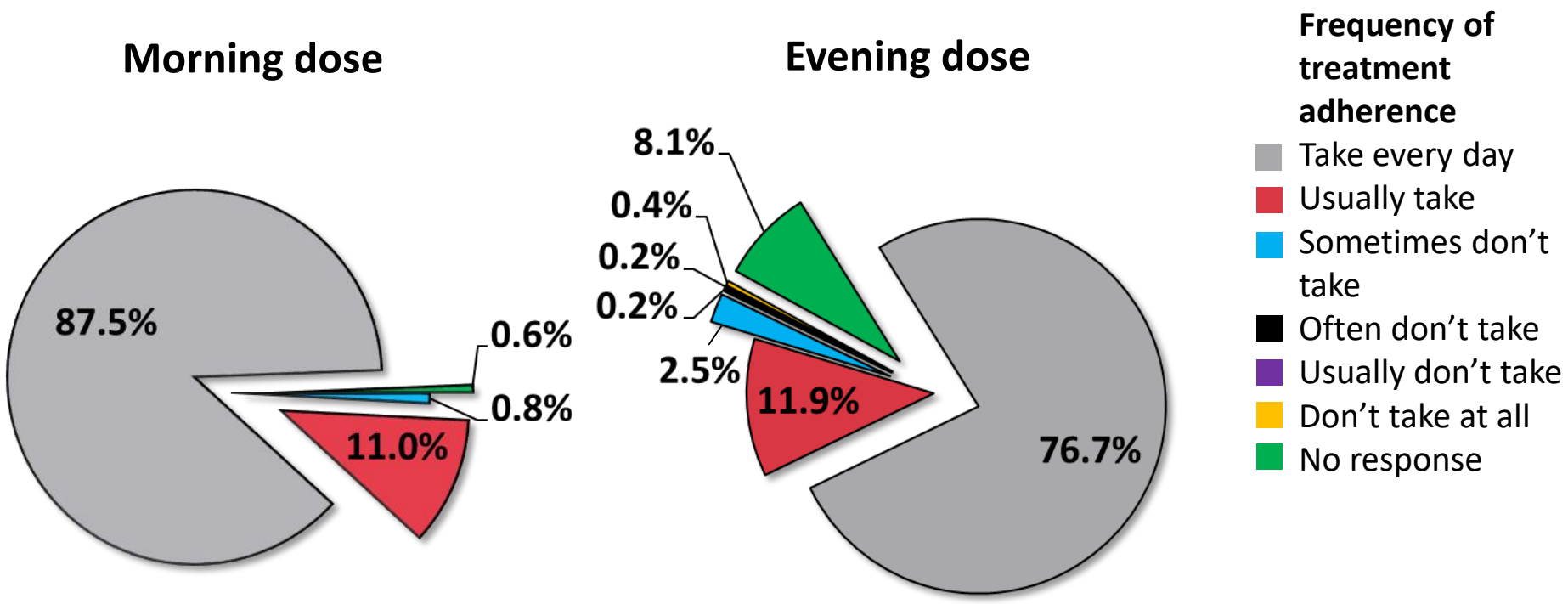
Mean daily number of medications taken by transplant patients



Daily medication intake was a lifestyle restriction in >20% of transplant recipients and was the most common barrier to non-adherence

Morales JM, et al. Clin Transplant 2012;26(2):369–76

Kidney transplant patients are more likely to take their morning dose than their evening dose

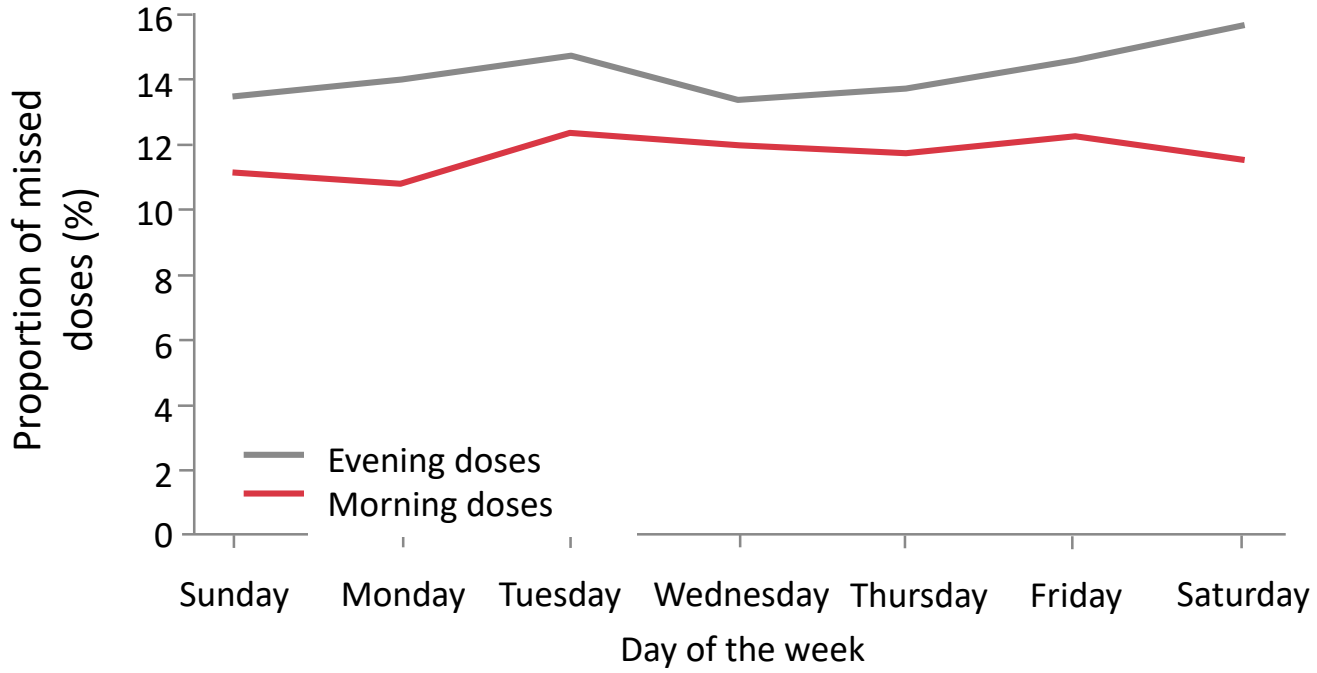


Adherence rate was lower for the evening dose than the morning dose ($p<0.001$)* and decrease in adherence rate with time was more pronounced for the evening dose

*Based on difference in proportion of responses "take the drug every day" for morning vs. evening doses
Adapted from Ichimaru N, et al. Transplant Proc 2008;40(5):1362–5

Evening dose is missed most frequently with tacrolimus in stable kidney transplant patients

Percentage of missed doses with tacrolimus split by morning versus evening dose and day of the week

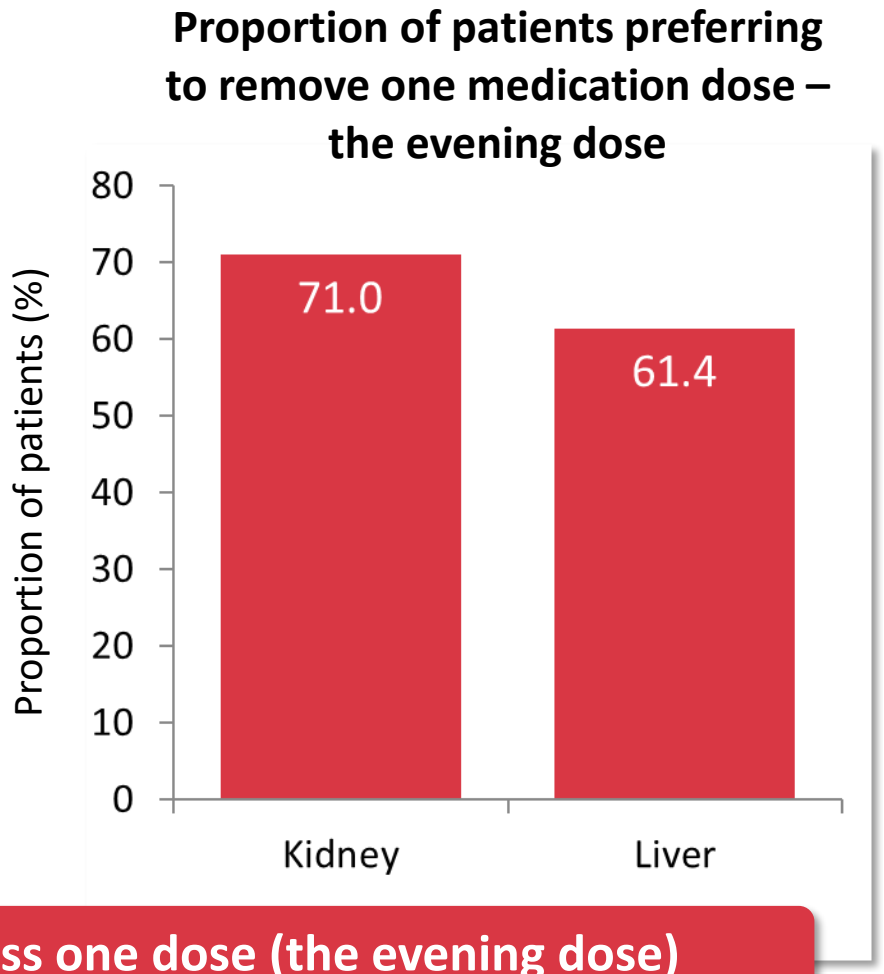


Mean percentage of missed doses was higher in the evening than in the morning (14.2% vs. 11.7%, respectively, p=0.0035)

Adapted from Kuypers DR, et al. Transplantation 2013;95(2):333–40

Kidney and liver transplant recipients prefer to reduce dosing frequency and remove the evening dose

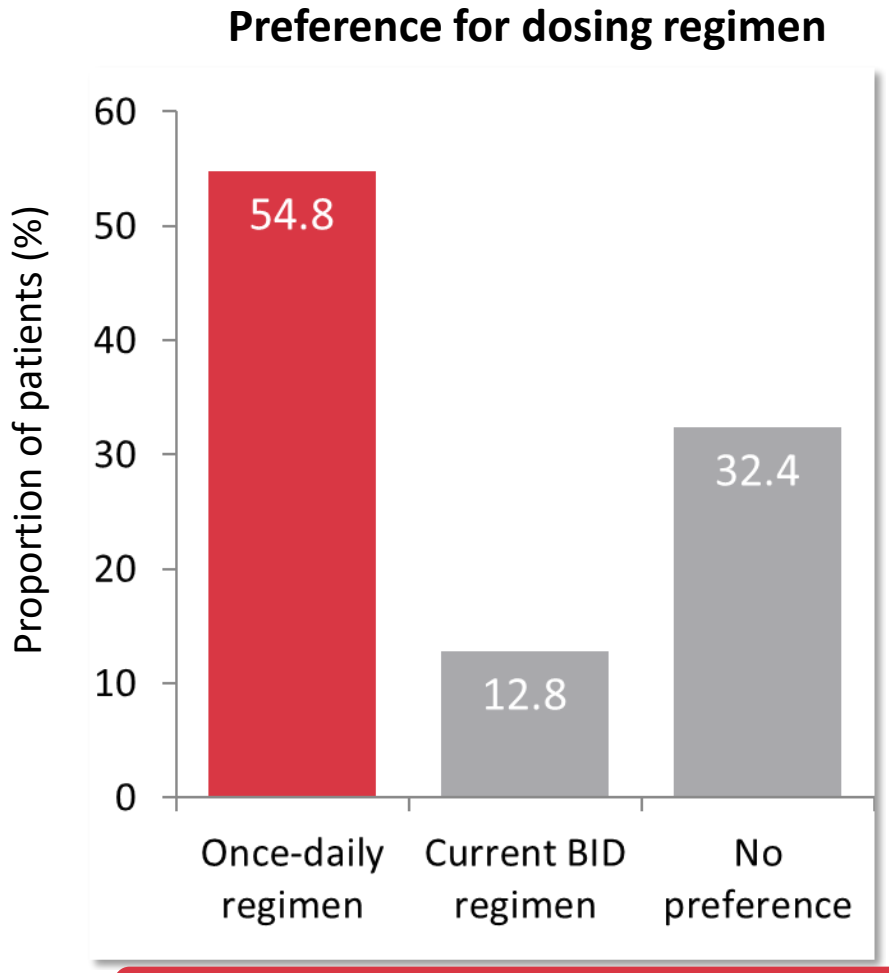
- Most common barriers to adherence in kidney and liver transplant recipients:
  - "having to take the immunosuppressant therapy too many times per day" (31.5% and 32.5%, respectively)
  - "having to take too many tablets...at one time" (31.5% and 27.0%, respectively)



Patients would prefer to suppress one dose (the evening dose)

Morales JM, et al. Clin Transplant 2012;26(2):369–76

Kidney transplant recipients prefer once-daily dosing



- The most common reasons for preferring a once-daily regimen were:
  - "reduce the burden of taking medication"
  - "prevent me from missing a dose"
  - "be easier to have a regular medication time"

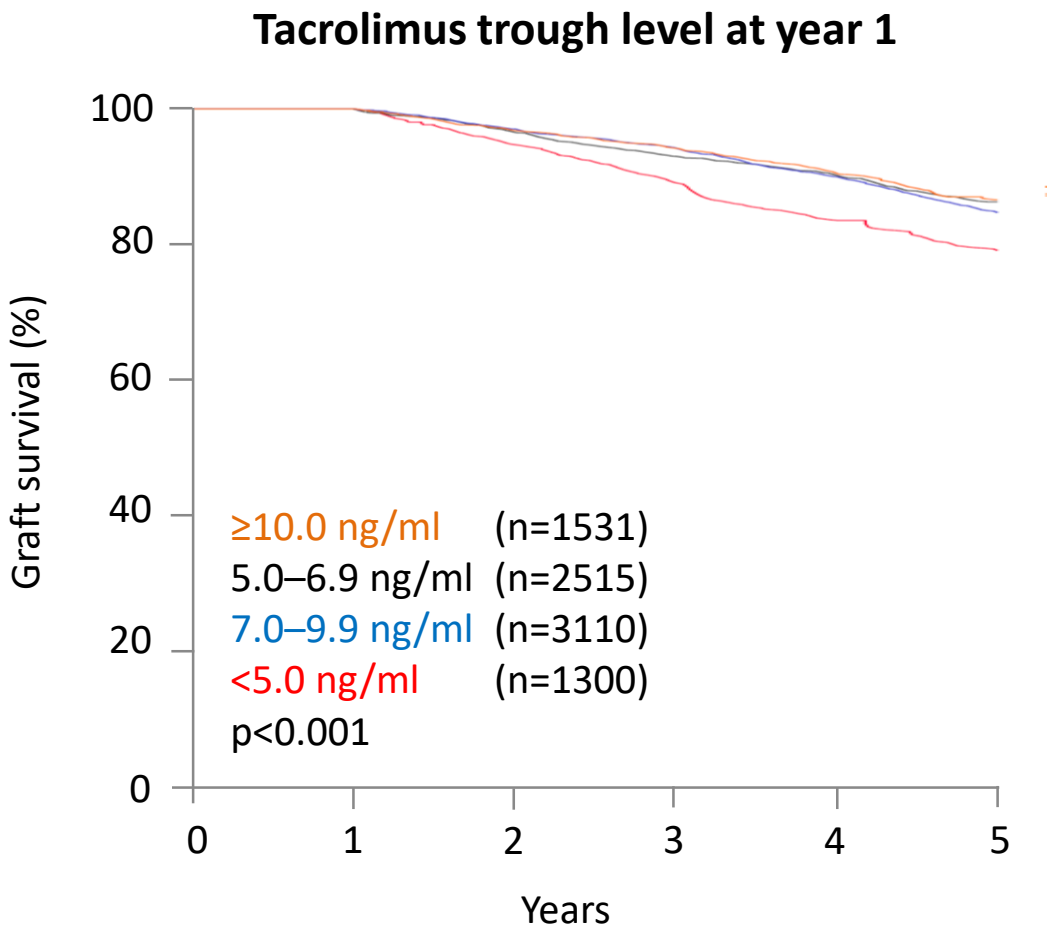
Most patients (54.8%) prefer a once-daily dosing regimen

BID, twice daily

Ichimaru N, et al. Transplant Proc 2008;40(5):1362–5

Sub-optimal immunosuppression

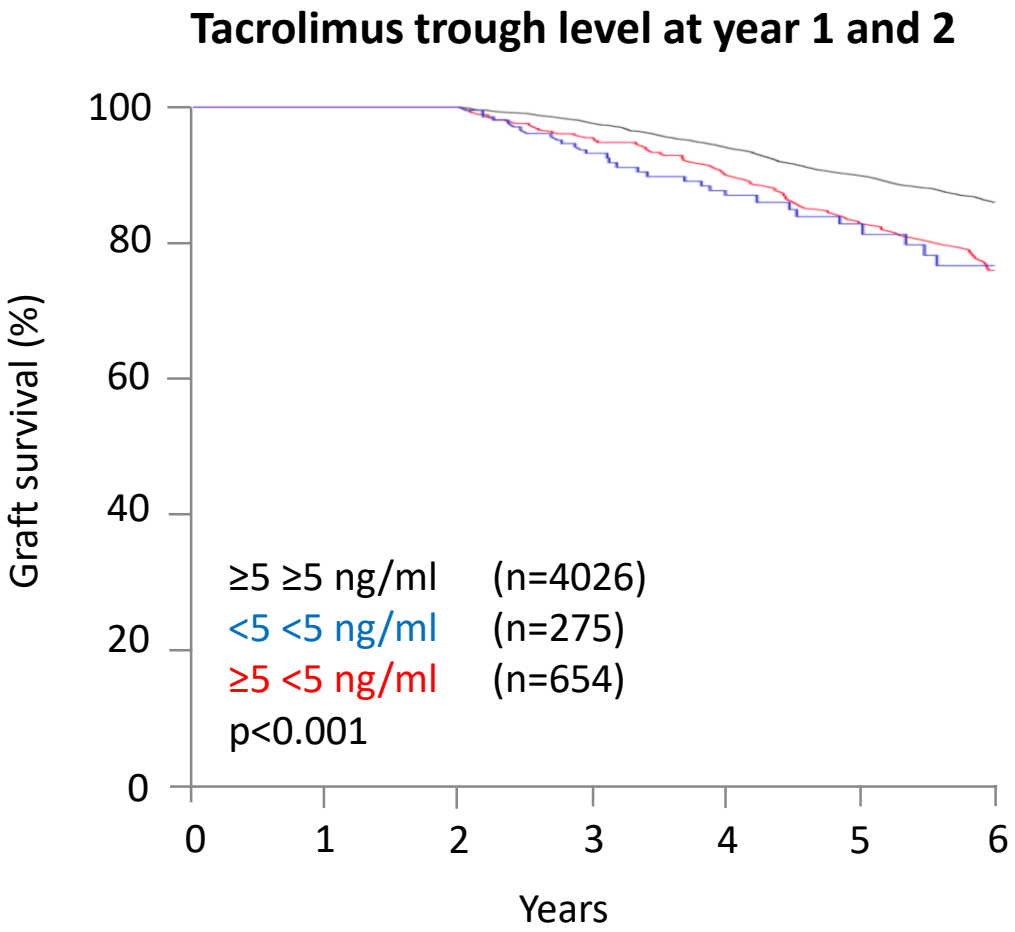
Tacrolimus trough level ≥5 ng/ml provides better graft survival



1-year tacrolimus trough level <5 ng/ml was associated with inferior graft survival (p<0.001)

Adapted from Opelz G. Tacrolimus trough levels and kidney graft survival. Newsletter 1: 2014. Available at: www.ctstransplant.org/public/newsletters/2014/png/2014-1.html?ts=2891094340847155. Accessed October 2015

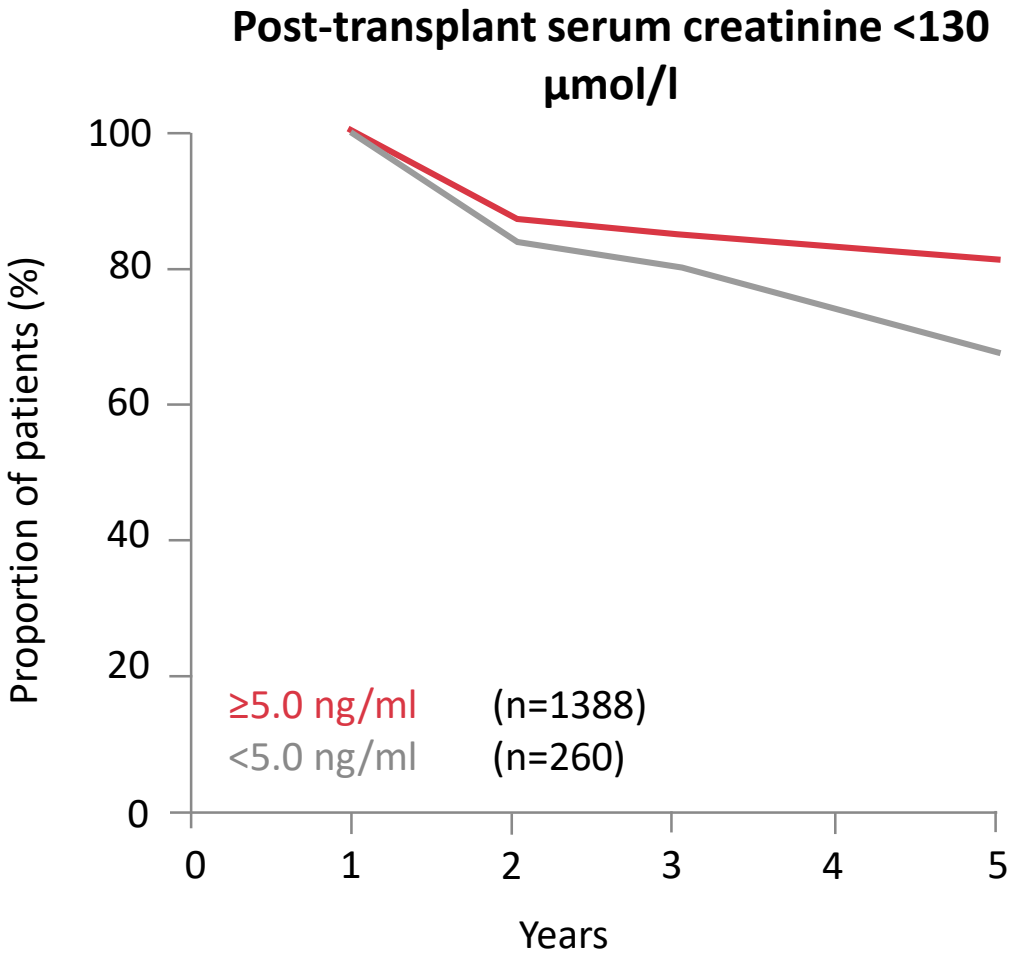
Reducing tacrolimus trough level to <5 ng/ml during year 2 is associated with reduced long-term kidney allograft survival



Graft survival during years 3–5 post-transplant was inferior in patients whose 2-year trough level was <5 ng/ml (p<0.001)

Adapted from Opelz G. Tacrolimus trough levels and kidney graft survival. Newsletter 1: 2014. Available at: www.ctstransplant.org/public/newsletters/2014/png/2014-1.html?ts=2891094340847155. Accessed October 2015

Tacrolimus trough level <5 ng/ml associated with reduced long-term kidney allograft function

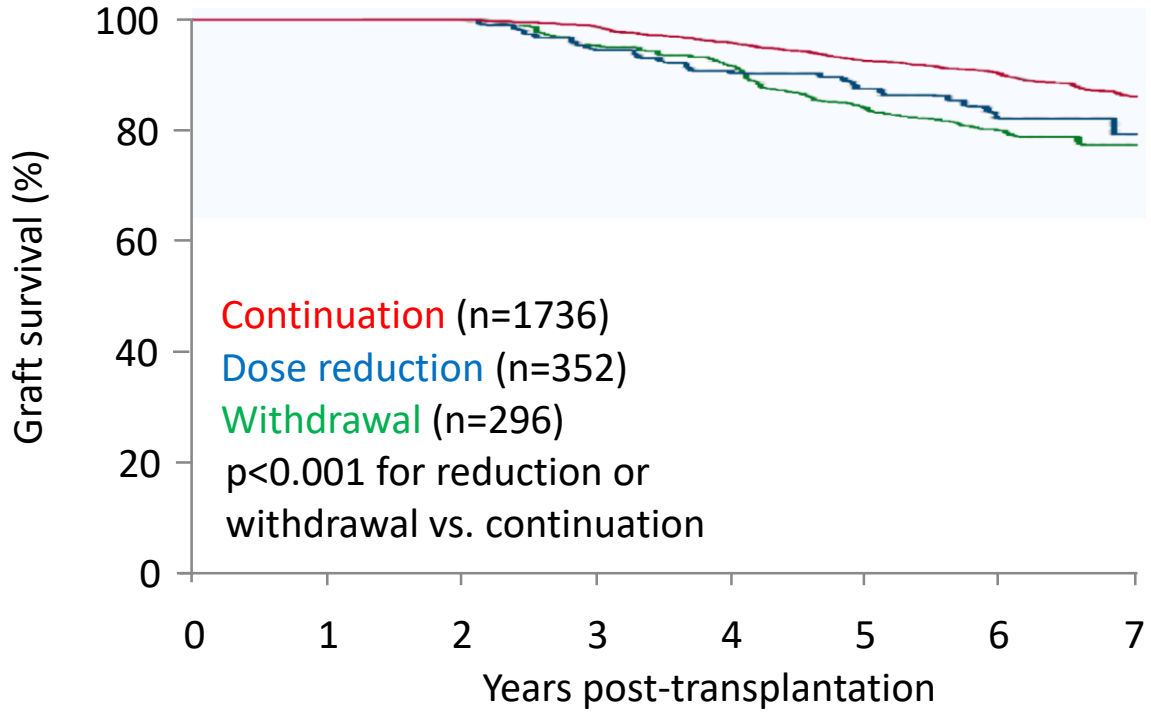


Tacrolimus trough level <5.0 ng/ml is associated with a decline in the proportion of patients with excellent graft function up to 5 years post-transplant

Adapted from Opelz G. Tacrolimus trough levels and kidney graft survival. Newsletter 1: 2014. Available at: www.ctstransplant.org/public/newsletters/2014/png/2014-1.html?ts=2891094340847155. Accessed October 2015

Dose minimisation or withdrawal of tacrolimus increases the risk of graft loss in kidney transplantation

Kidney graft survival by tacrolimus dose continuation, reduction, or withdrawal



Graft survival during years 3–7 was significantly impaired with tacrolimus dose reduction to ≤2.0 mg/day (HR 1.65, p=0.004) or withdrawal (HR 1.52, p=0.027) during year 2 post-transplant

HR, hazard ratio

Adapted from Opelz G, et al. Transplantation 2008;86(3):371–6

Summary

- IPV in systemic is a significant variable associate with long term graft survival.
- Sources of IPV are: Pharmacogenetics and Adherence
- Formulations that deliver drug before or after proximal small bowel show decreased IPV
- Decreasing frequency of dosing has shown significant improvement in adherence.
- Recent CTS data indicates that targeting tacrolimus exposure (< 5 ng/mL) in first year or reduction in the second year is associated with worst graft survival