

Extended-Release Tacrolimus and Medication Adherence After Transplantation

Mahsa Hosseini chimeh

Assistant professor of nephrology

Labbafinejad hospital



Case :

- 32-year-old woman
- 3 years post-transplant
- Tacrolimus BID
- Works full-time
- Frequently forgets evening dose
- Creatinine 1.0 → 1.8 mg/dL
- Tacrolimus levels: 4, 11, 5, 10, 3, 9 ng/mL
- New DSA detected
- Biopsy: chronic active antibody-mediated rejection
- No apparent pharmacologic interaction





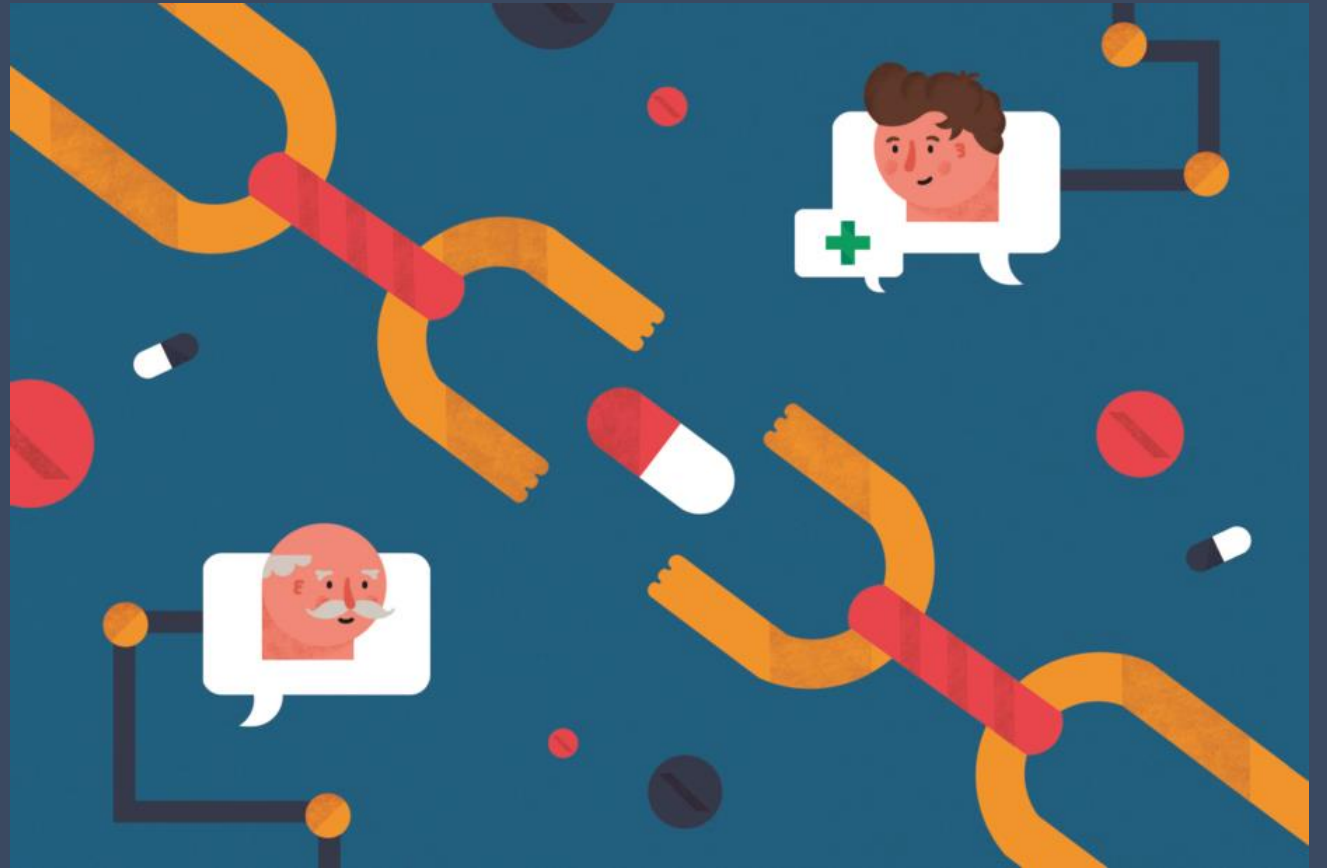
Nonadherence

Pharmacokinetic
variability



Nonadherence

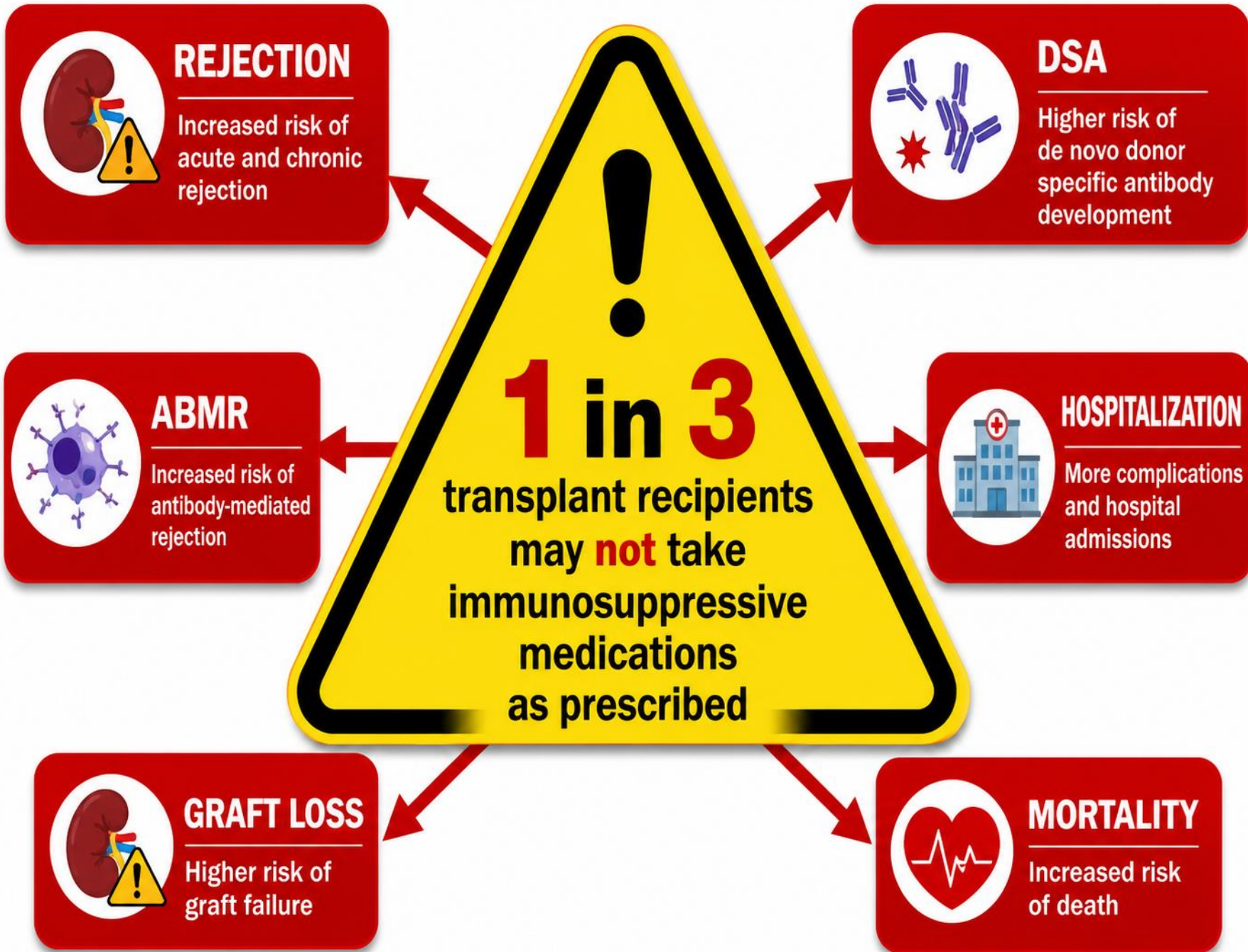
A patient failure to follow the recommended health care regimen



① 20–50% of kidney transplant recipients demonstrate some degree of medication nonadherence.

① Nonadherence is among the **strongest modifiable risk factors** for late graft loss.





Patient related factors

lack of visible symptoms

Knowledge deficit

Health beliefs : distrust to chemical

Psychological factors: denial , depression and anxiety , medication fatigue

Forgetfulness

Substance abuse



Medication related factors

"Even the best regimen fails if patients lack support, education, or resources."



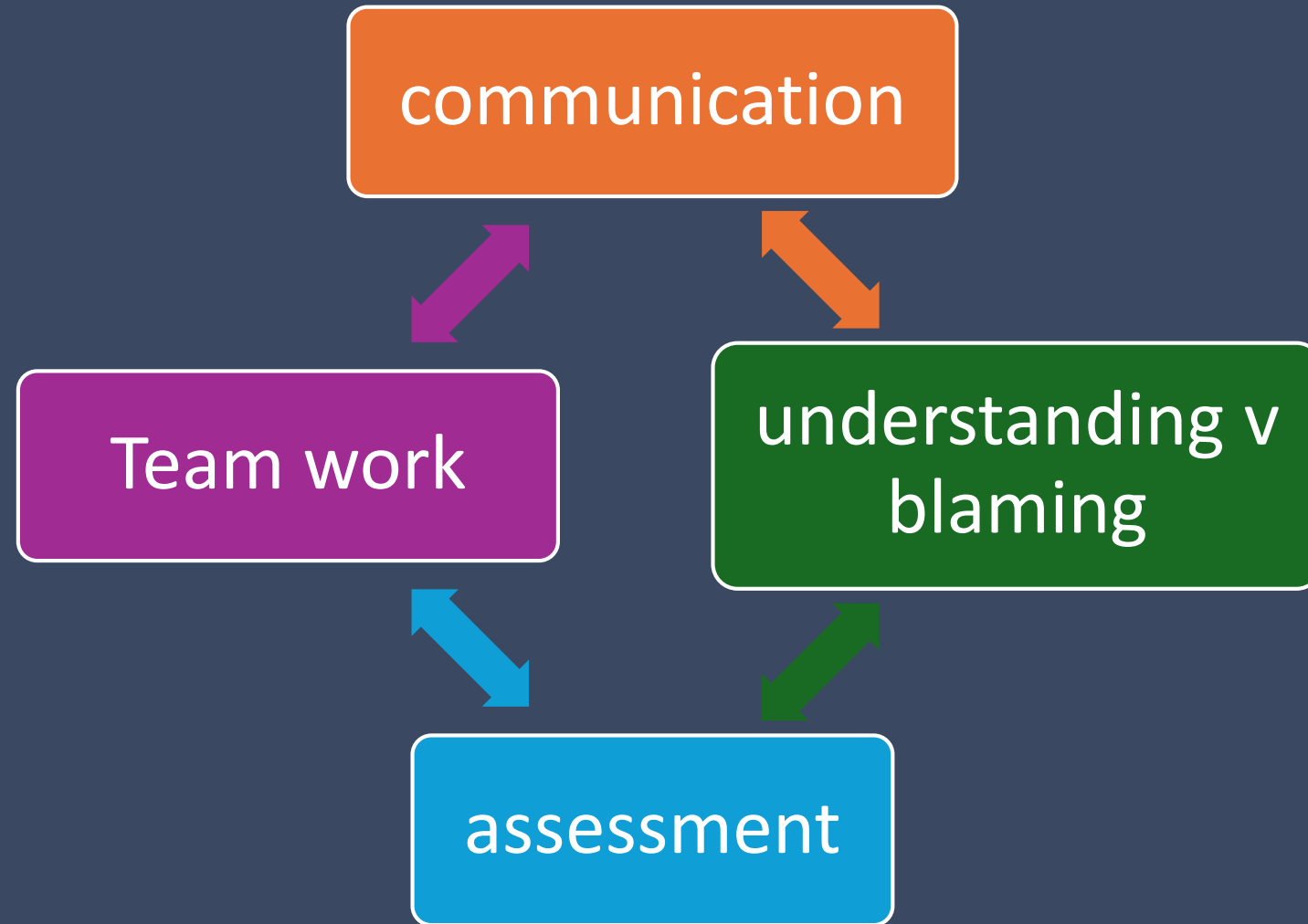
Social determinants of adherence

Socioeconomic and environmental factors

- Low health literacy
- Social support
- Financial strain
- Unstable living situation
- Cultural and language barriers



“Its not just the patients fault”



Assessment is key

- We must proactively **screen for nonadherence** using multiple methods
 1. Self report (open ended , non-judgmental questions)
 2. Pill count
 3. Drug levels

Cannot distinguish variability from deliberate dose timing changes.

4. Electronic Monitoring

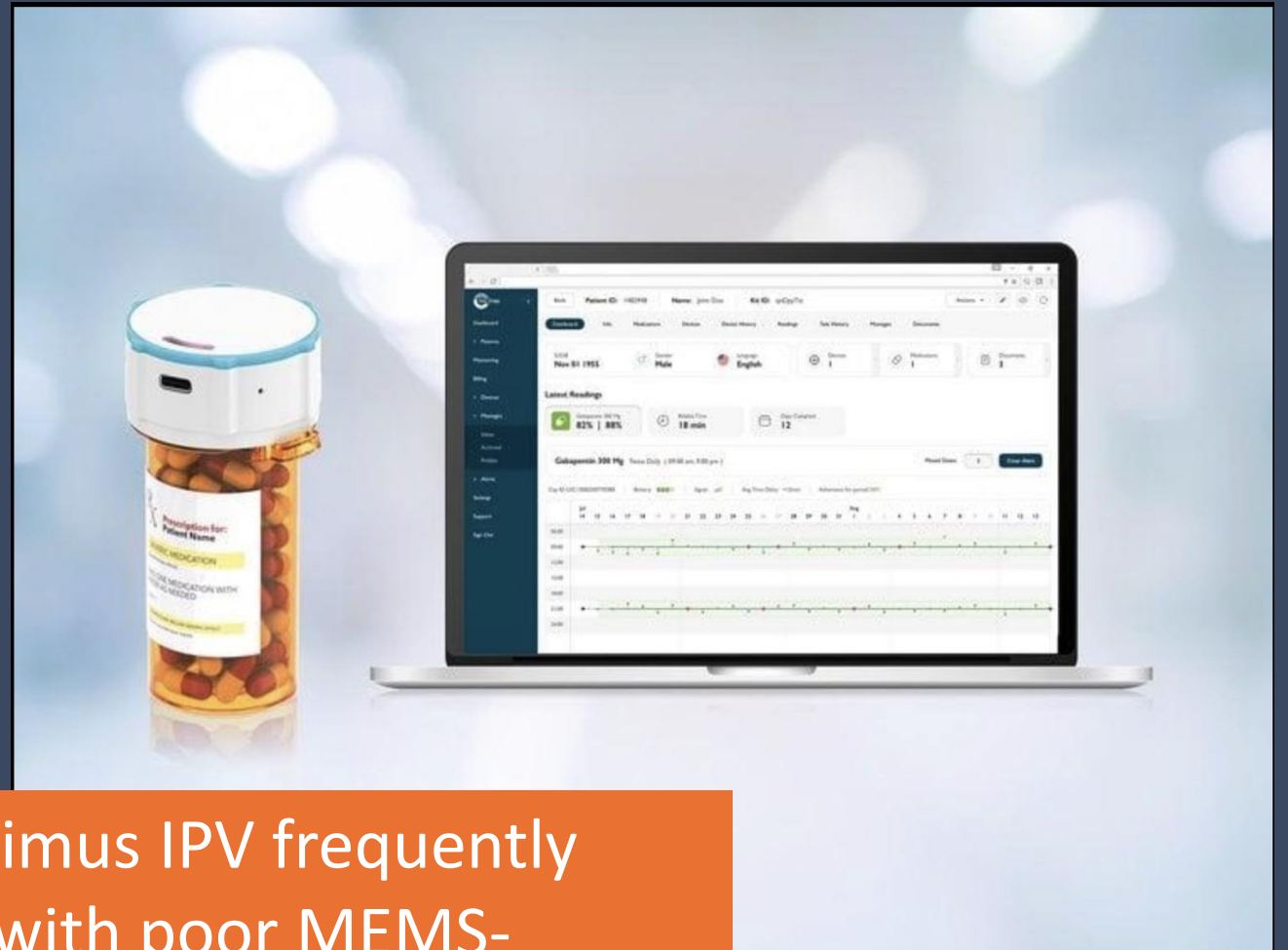
- MEMS caps (Medication Event Monitoring System)
- Most accurate adherence assessment.



MEMS caps

It is an electronic pill bottle cap that records every time the bottle is opened.

Most accurate adherence assessment.



High tacrolimus IPV frequently correlates with poor MEMS-recorded adherence.



- Screen for risk factors:
 1. Depression
 2. Low social support
 3. Financial problem
 4. Adolescents and Young adults
 5. Previous rejection
 6. Missed clinic appointments



THE GOAL : stable
immunosuppression or
tacrolimus level to be
consistently with in target
range

The reality :
levels often
fluctuate



Intra patient variability IPV

- Note:
- While nonadherence is a key driver, **high IPV** can occur even in **adherent patients** due to pharmacokinetic variability, making it a broader biomarker of **instability**.



IPV (intra patient variability)

- With-in patient ,fluctuation in drug level over time .

whitch one is more accurate?

Mean

Standard deviation

coefficient of variation (CV%)



Patient A

Month	Tac Level
Jan	7
Feb	7
Mar	7
Apr	7

Mean = 7 ng/mL

CV = 0%

Patient B

Month	Tac Level
Jan	3
Feb	11
Mar	4
Apr	10

Mean = 7 ng/mL

CV \approx 50%



LEVEL(x)	(x-MEAN)	(X-MEAN) ²
7.2	0.03	0.0009
5.1	-2.07	4.2849
9.8	2.63	6.9169
6	-1.17	1.3689
10.5	3.33	11.0889
4.4	-2.77	7.6729
	SUM	31.3334

$$SD = \sqrt{31.3334/5} = 2.5$$

$$CV\% = SD/MEAN \times 100 = 34\%$$

Standard deviation (SD)

$$T_{ac}SD_i = \sqrt{\frac{\sum_i (C_{0ij} - \bar{C}_0_j)^2}{n_j - 1}}$$

- Measures spread of values around the mean
- Higher value of SD = higher variability

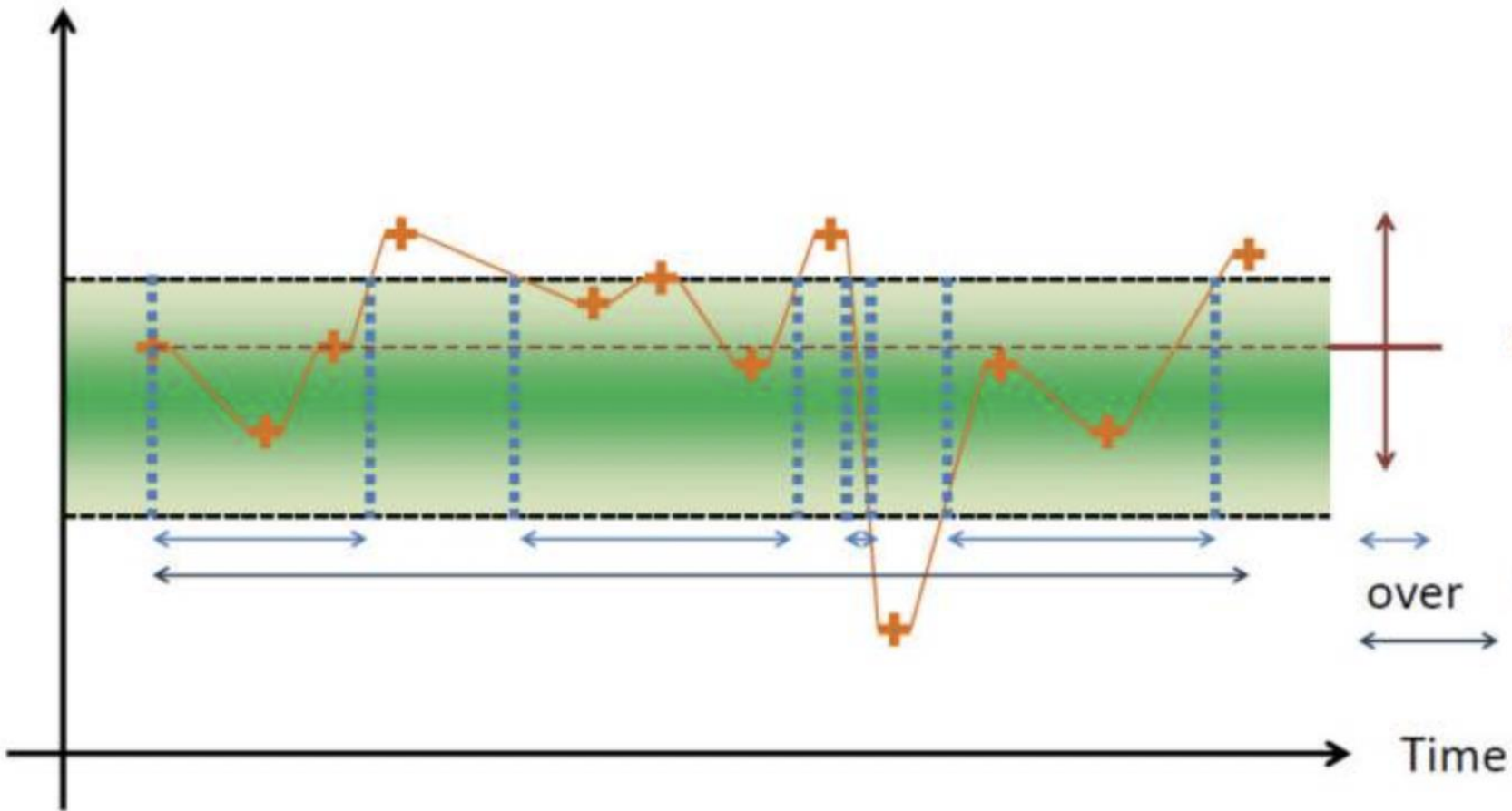
Coefficient of variation (CV)

$$CV (\%) = \frac{SD}{mean} \times 100$$

- Ratio of the SD to the mean, expressed as %
- Higher % CV = higher variability



Concentration



$$\frac{SD}{\text{mean}} = \mathbf{CV (\%)}$$

= Mean \pm **SD**

over = **TTR (%)**

- \leftrightarrow : time in the range
- \longleftrightarrow : total time





Tools

You are here: [Home](#) > [Tools](#) > [IPV Calculator](#)

Tools

[Thrombodynamic ratio \(TDR\) calculator](#)

[Tacrolimus IPV calculator](#)

Tacrolimus IPV Calculator

Please note: This tool is primarily for research/audit use. Before using it for patient management, please validate it fully. The CET can take no responsibility for adverse clinical events arising from these use of this calculator.

This tool calculates the inpatient variability (IPV) of dose-corrected tacrolimus levels. It requires a minimum of 3 tacrolimus levels (with corresponding doses). The formula used is the Mean Absolute Deviation (MAD) expressed as a percentage.

Data

Dose

Concentration

+

 Calculate

Output

Enter a minimum of 3 tacrolimus doses/concentrations, and click the calculate button.



CV > 30-40% is associated with
poor clinical outcome

Increased risk
of acute
rejection

Higher rates of
de novo DSA

Nephrotoxicity

Graft loss and
reduced long
term survival



- Multiple studies demonstrated that high tacrolimus **IPV (CV>25- 30%)** or **SD> 2** is significantly associated with **increase risk of kidney allograft rejection and loss .**



Factors Influencing IPV

1- non adherence

2- genetic factors : CYP3A5 polymorphism

3- drug – drug interaction

4- formulation change

5- clinical variable : hematocrit, albumin

6- GI function : malabsorption , bariatric surgery , gastroparesis , diarrhea









Transplantation Reviews

Supports open access

Factors and interventions affecting tacrolimus intrapatient variability: A systematic review and meta-analysis

Hongsheng Chen ^{a b} , Shuang Liu ^a, Lingling Yu ^{a b}, Xiaofei Hou ^c, Rongsheng Zhao ^a   [Show more](#) 




Cite



Add to Mendeley



Share

10.1016/j.trre.2024.100878 

cytochrome P450 3A5 (CYP3A5) expressers
nonadherent patients
proton pump inhibitors or statins,
Black or African American recipients,

recipients consuming extended-release formulation exhibited lower IPV.



Can Once-Daily Tacrolimus Improve Adherence?



Meta-Analysis

> Eur J Clin Pharmacol. 2018 Oct;74(10):1249-1260.

doi: 10.1007/s00228-018-2512-7. Epub 2018 Jun 30.

Extended release versus immediate release tacrolimus in kidney transplant recipients: a systematic review and meta-analysis

Comparing between the two tacrolimus formulations, there were no significant differences of eGFR, CrCl, Scr, BPAR, graft survival, and patient survival at different times over 4 years after transplantation.



Epub 2024 Apr 29.

Evaluation of Tacrolimus Concentrations and Clinical Outcomes Between Extended and Immediate Release Formulations in Kidney Transplant

Conclusions: The time to therapeutic tacrolimus levels did not differ based on tacrolimus formulation and was not correlated with clinical outcomes.



> Clin Transplant. 2023 Jan;37(1):e14840. doi: 10.1111/ctr.14840. Epub 2022 Nov 27.

Outcomes in kidney transplant recipients treated with immediate-release tacrolimus capsules versus extended-release tacrolimus capsules: A cohort study

KTRs treated with IR-TAC capsules had an increased hazard of experiencing the composite outcome when compared to patients treated with ER-TAC capsules; however, this result was not significant



"Extended-release tacrolimus is not a cure for nonadherence, but it removes one important barrier: regimen complexity."



Take-Home Messages

- A functioning graft depends on **consistent immunosuppression**, not just therapeutic tacrolimus levels.
- Nonadherence remains one of the most **preventable causes** of late graft failure.
- **High IPV** may reveal hidden problems **before rejection** occurs.
- **Once-daily tacrolimus** can **simplify** treatment and **reduce barriers** to adherence.
- **Every missed dose matters, and every effort to improve adherence matters.**



Once-Daily Tacrolimus

Simplifying Today, Protecting Tomorrow



Improved adherence
Fewer missed doses



Greater convenience
Better quality of life



Stable immunosuppression
Less variability, more protection



Better outcomes
For our patients' long-term health



**One dose.
One goal.
ONE HEALTHY GRAFT**

Thank you
for your attention



Every effort for adherence today leads to a healthier tomorrow for our patients.

Better Adherence ✓

Stable Exposure

Stronger Protection

Better Outcomes

