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**Therapeutic Drug Monitoring
and Clinical Toxicology**



Société Française de
Pharmacologie et de Thérapeutique

**IATDMCT
& SFPT
2026**

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RENNES
COUVENT DES JACOBINS

Missed dose management : Beyond “Skip or Take”

A universal population half-life rule for missed and delayed oral doses

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A daily question, binary answers

≈ 50 %

of patients with chronic conditions take fewer than half of their doses correctly

“Skip or take”

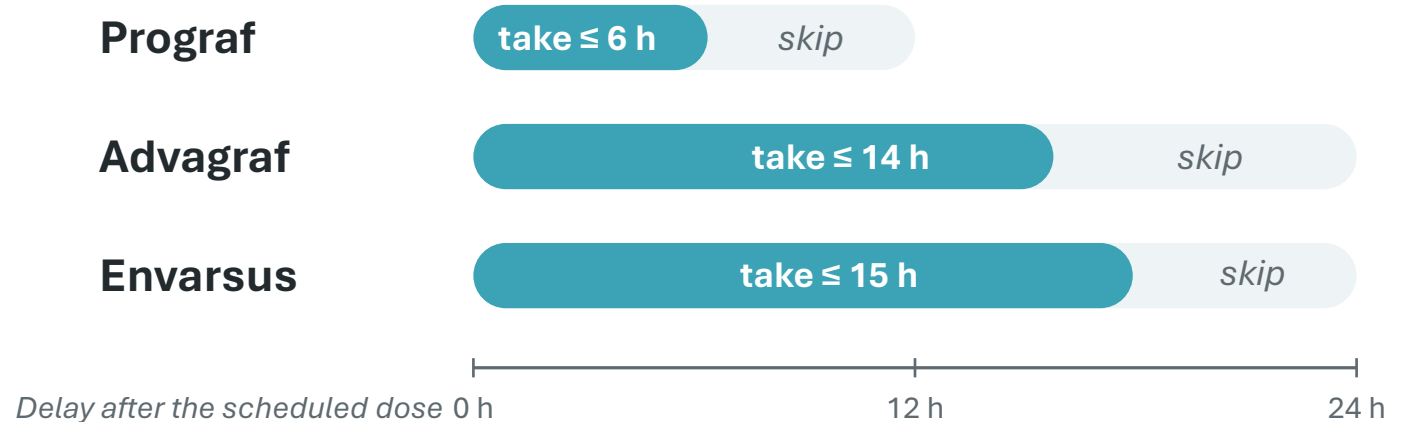
labels reduce a continuous PK problem to an all-or-nothing cutoff

No framework

no universal, PK-grounded catch-up rule

Empirical cutoffs, different between FDA and EMA

One molecule — tacrolimus — three answers



Amiodarone: “unless it is nearly time” — no number



One equation, three variables, a graded dose

τ dosing interval

$t_{1/2}$ population half-life

d delay

Catch-up dose = usual dose $\times$ max(M, S)

$$M = 2^{-d / t_{1/2}}$$

Dose fraction remaining at the time of the delay

$$S = (1 - 2^{-(\tau-d) / t_{1/2}}) / (1 - 2^{-\tau / t_{1/2}})$$

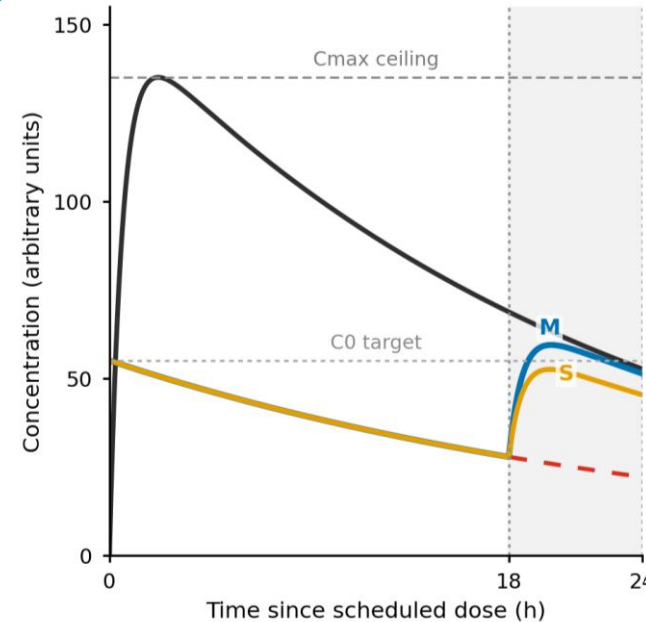
Dose fraction adjusted for the remaining interval to limit accumulation

Then rounded down to the available strength

Concentration time curves in different scenarios

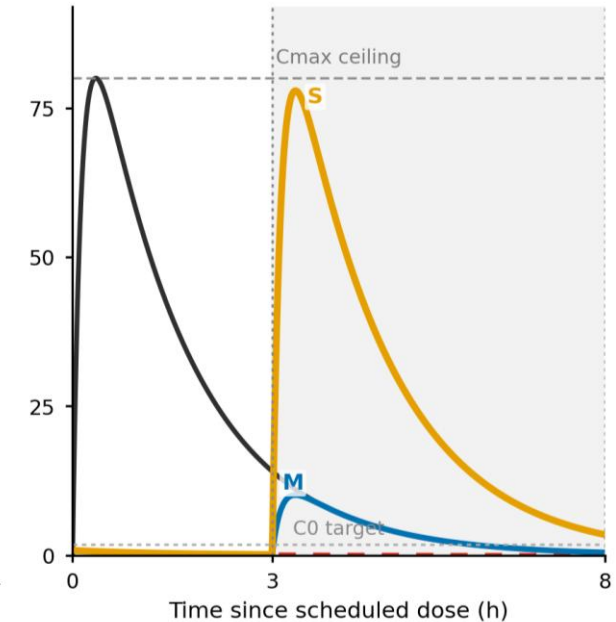
A M-dominant case (tacrolimus-like)

$t_{1/2} = 15.6$ h, $\tau = 24$ h, delay = 18 h



B S-dominant case (amoxicillin-like)

$t_{1/2} = 1$ h, $\tau = 8$ h, delay = 3 h

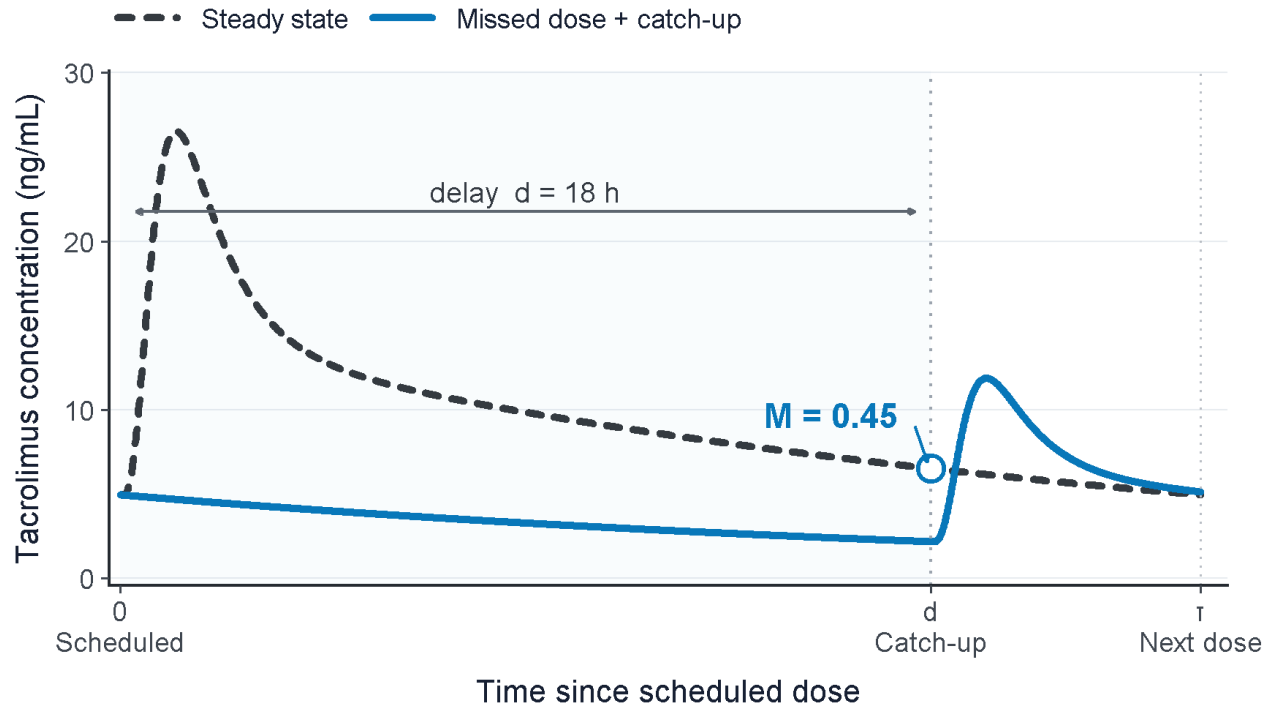


— Steady-state reference — Catch-up dose scaled by M (maintenance term)
- - Missed dose, no intake — Catch-up dose scaled by S (safety term)



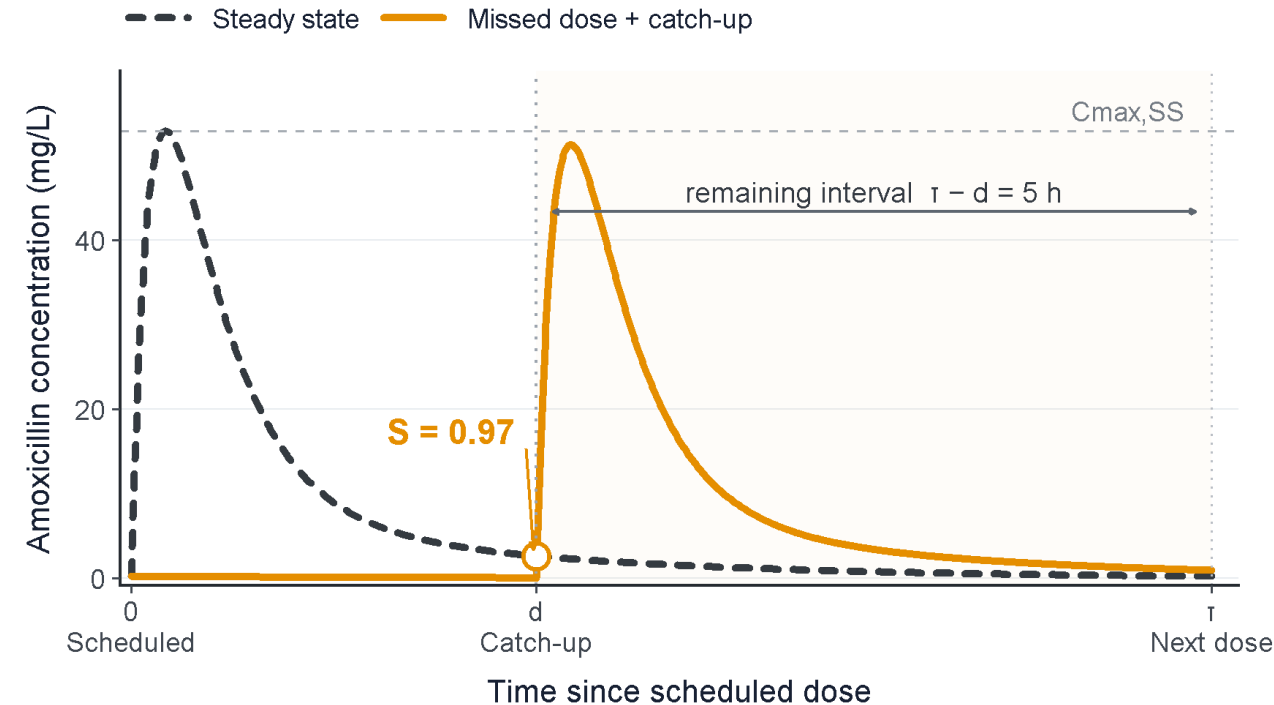
One equation, three variables, a graded dose

What is M : Tacrolimus example



M is the fraction of the dose that would still be on board at delay d , had it been taken on schedule

What is S : Amoxicillin example

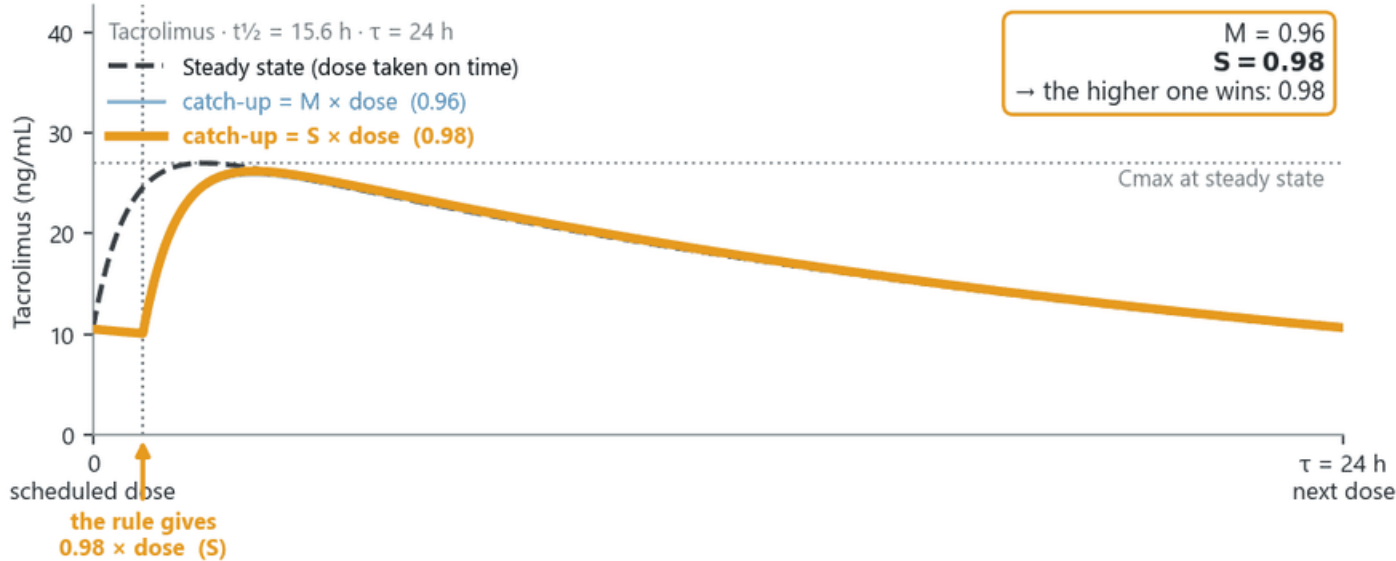


S is the largest fraction you can still give now without pushing the next scheduled dose above its steady-state peak.



One equation, three variables, a graded dose

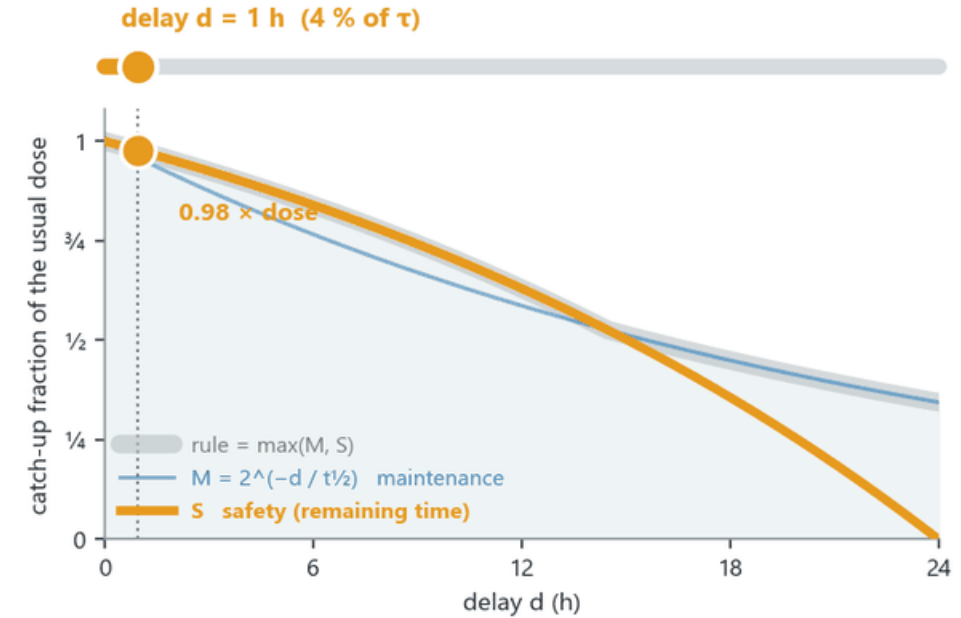
Tacrolimus — two candidate catch-up doses: $M \times \text{dose}$ and $S \times \text{dose}$



M is the fraction of the dose that would still be on board at delay d , had it been taken on schedule

S is the largest fraction you can still give now without pushing the next scheduled dose above its steady-state peak.

The rule follows the higher one: $\max(M, S)$



4 — auto-play GIF (delay sweeps 4 → 96 % of τ and back, ~11 s loop)

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2026

Stress-tested across 11 oral drugs

1

1,000 virtual patients

per drug, from published popPK models

2

One event

the dose is delayed, from slightly to fully missed

3

3 strategies

- half-life rule
- label cutoff
- skip

4

Exposure vs steady state

- AUC (primary)
- peak
- trough



The rule stays on target where labels fall off the cliff

% in target

averaged over all drugs and delays

Half-life rule

97.7 %

Label

81.7 %

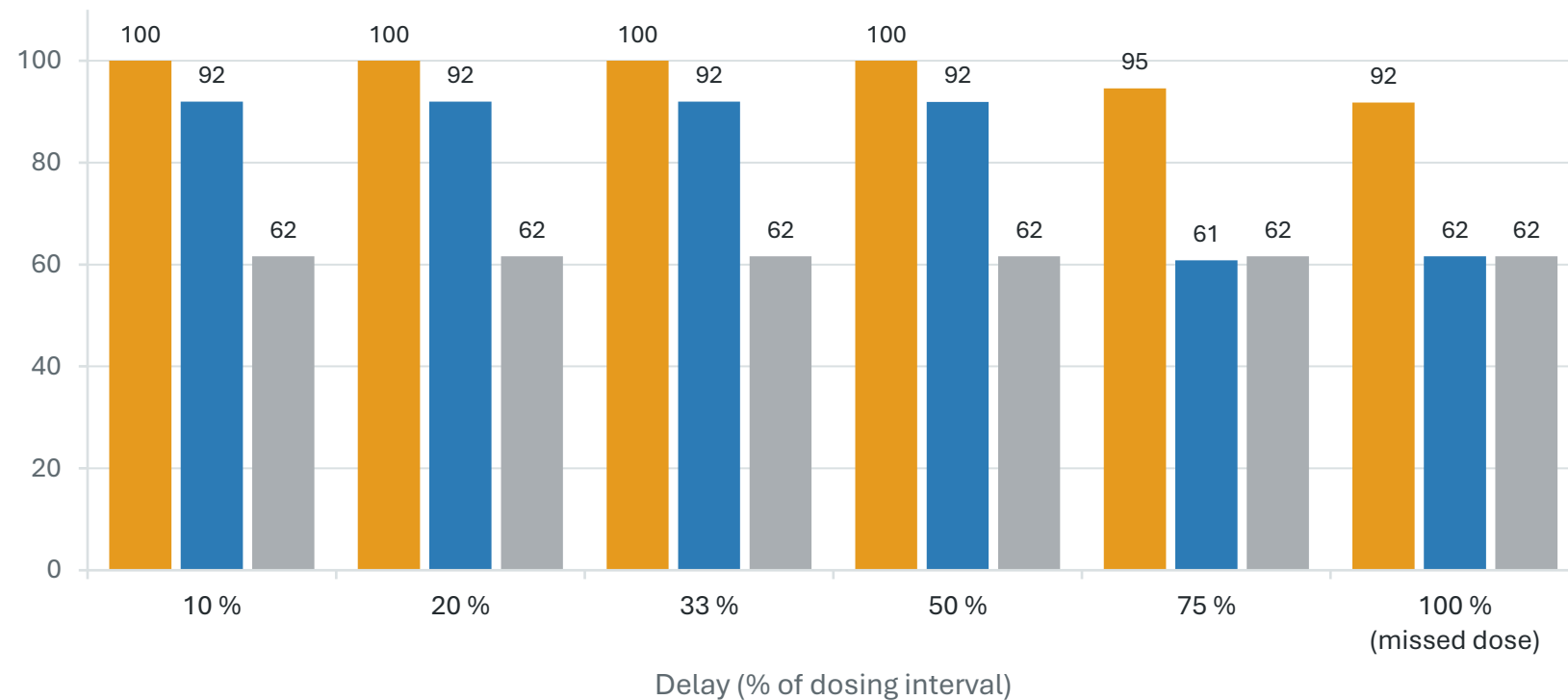
Skip

61.6 %

100 % on target through half an interval

The gain is where labels say “skip”

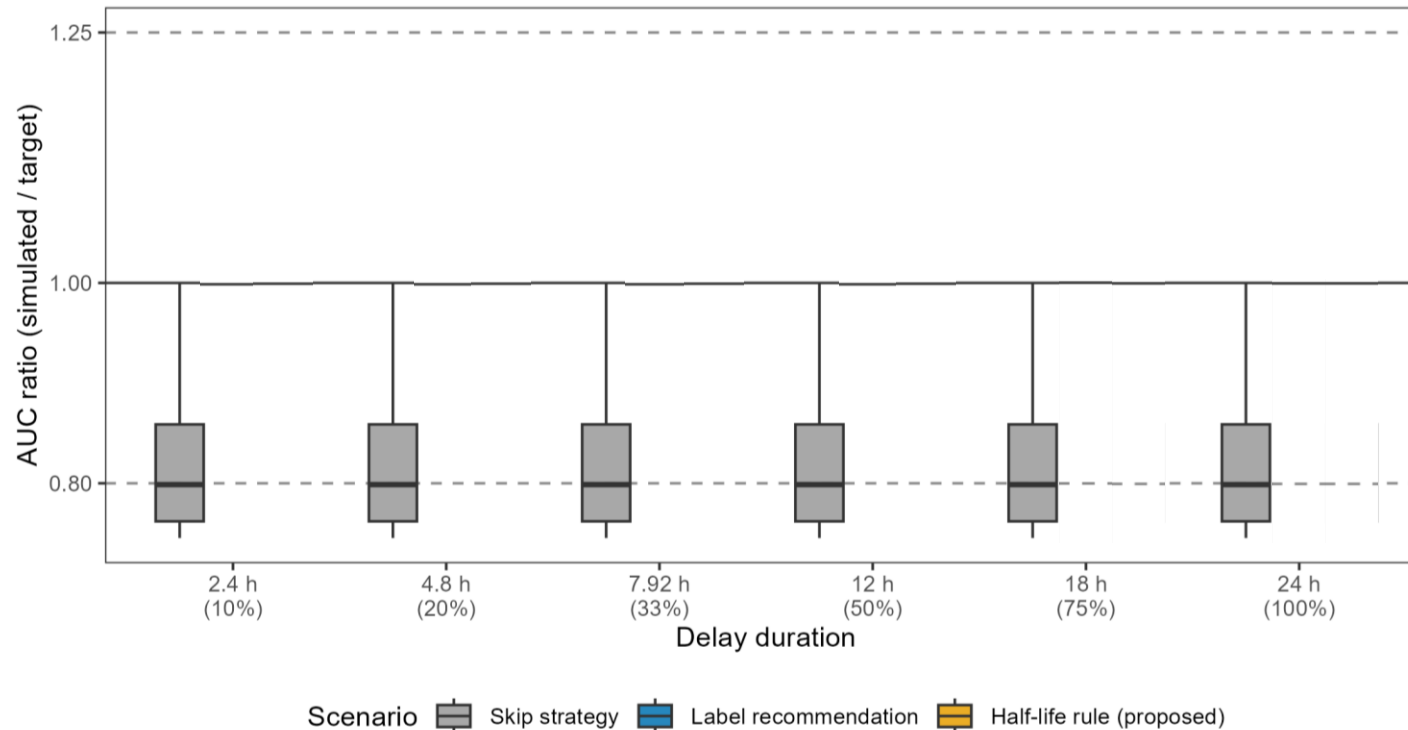
Patients with AUC in target after the event (%)



Half-life rule Label Skip

A practical example: levofloxacin once daily

Impact of dosing strategy on exposure recovery



The Skip

- Always skip → underexposure

The Label

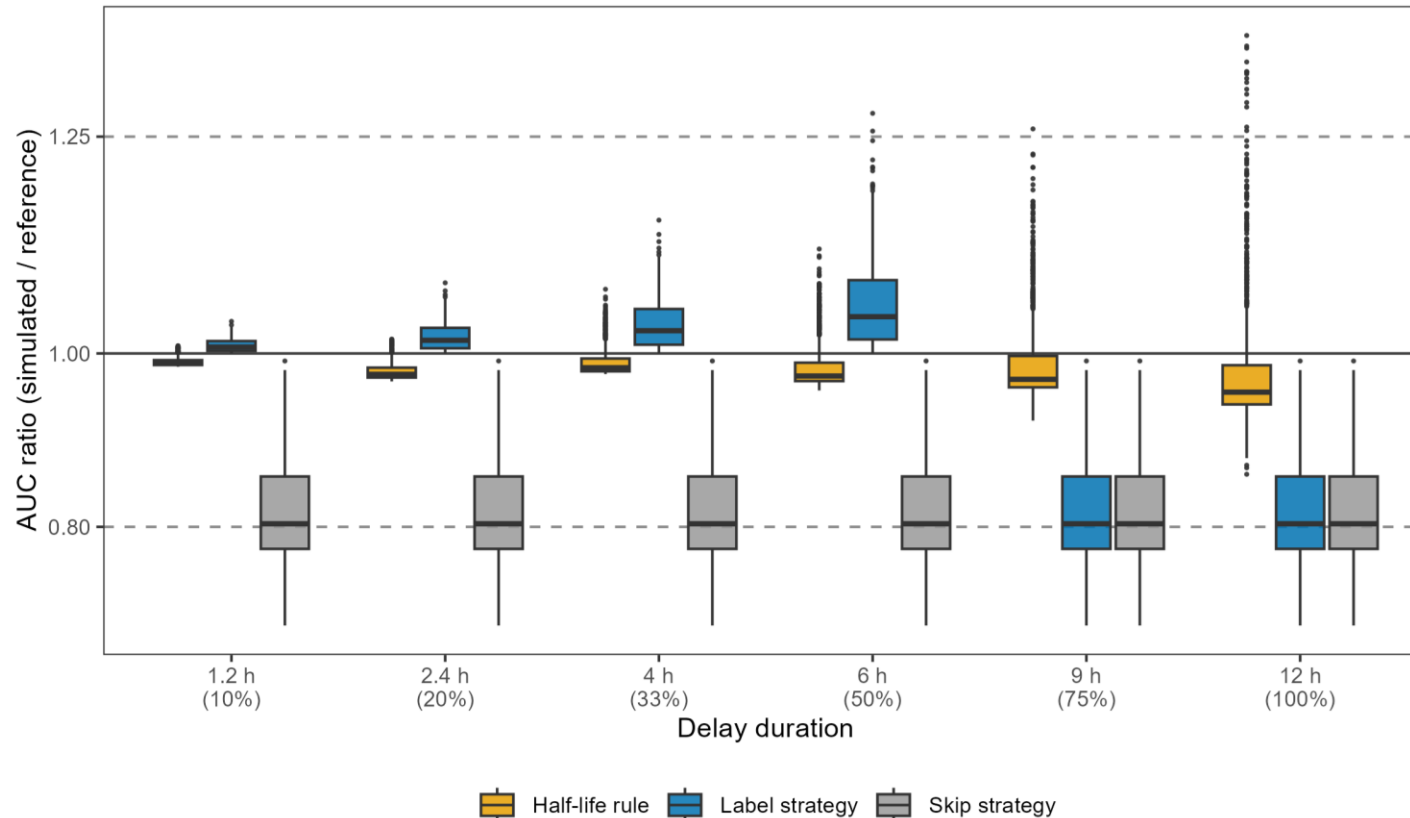
- Full dose just before the cutoff → overexposure
- Skip just after → underexposure

The Rule

- Half a tablet, whatever the delay up to half a day**
→ stays inside the window
Dose rounded down.

A practical example: tacrolimus twice daily

Impact of dosing strategy on exposure recovery



The Skip

- Always skip → underexposure

The Label

- Full dose just before the cutoff → overexposure
- Skip just after → underexposure

The Rule

- **Half a tablet, whatever the delay up to half a day**
→ stays inside the window
Dose rounded down.

Dose granularity matters

- Coarse dose increments may force omission
- Smaller strengths, such as tacrolimus, allow the rule to track the calculated dose more closely

Take-home

Thank you

Funding DIGPHAT — France 2030 (ANR-22-PESN-0017)

1

Three variables always available

replaces “skip or take” across oral drugs

2

Recovers exposure where labels give up

in a safe manner

3

A decision aid, with safeguards

not a substitute for TDM; not yet validated in patients

4

Towards harmonized PK-grounded labels

and decision-support tools

Try the calculator



tdmhub.shinyapps.io/MissedDoseApp

free · includes a Safety-First mode



Take-home

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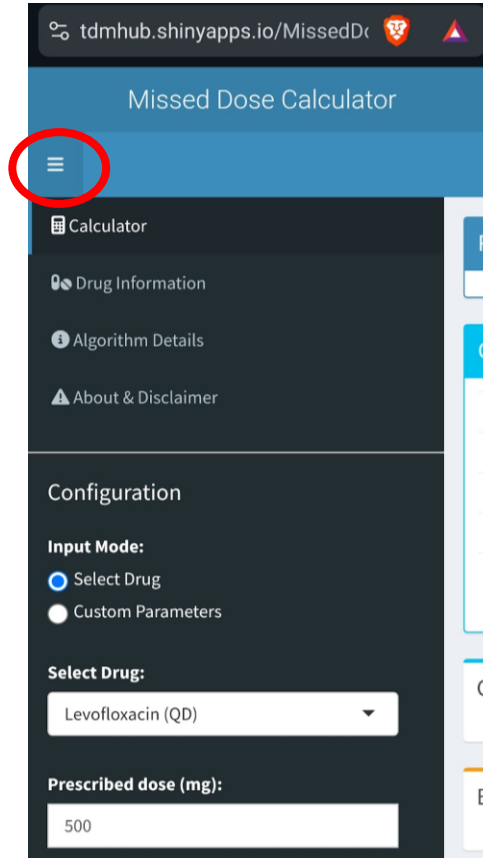
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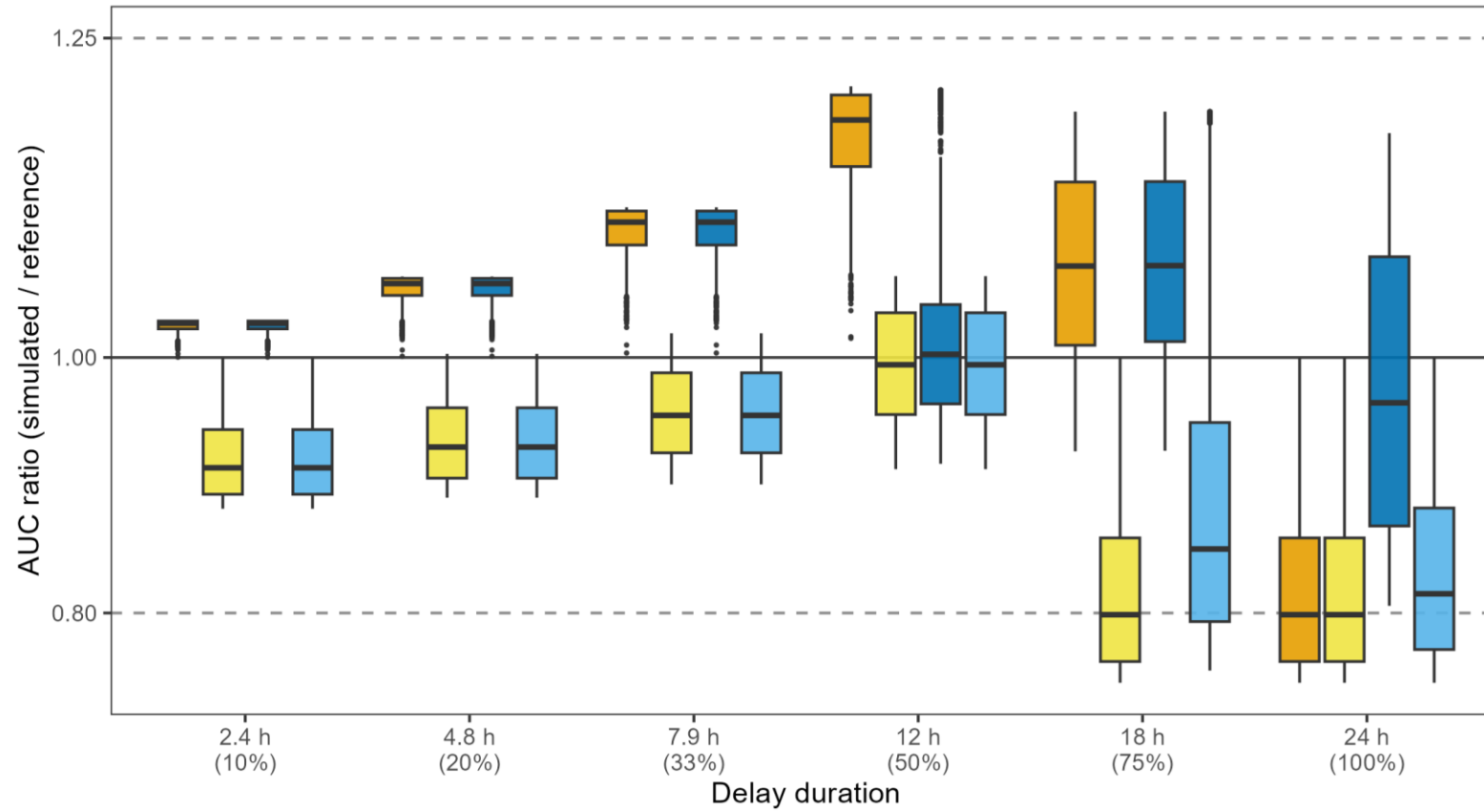


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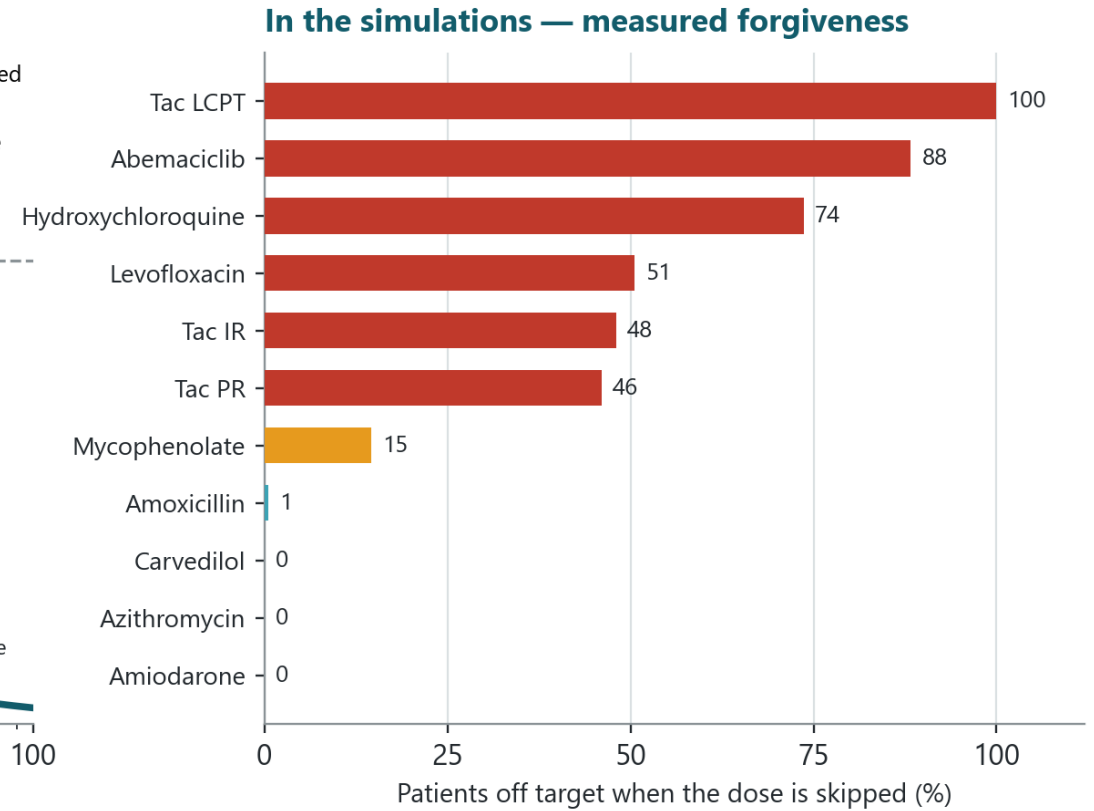
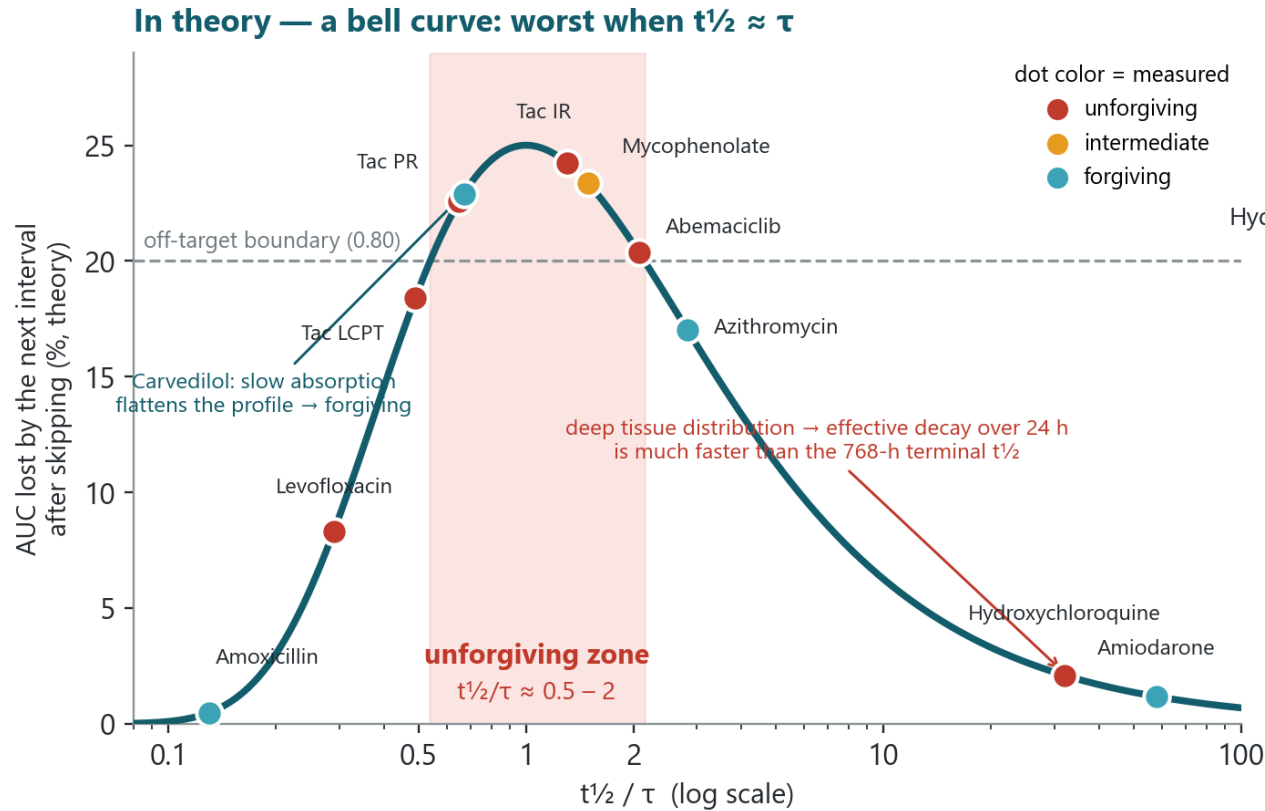
B Sensitivity analysis: parameter source and rounding



Algorithm settings

- Population ($t_{1/2}$) — round to nearest
- Population ($t_{1/2}$) — floor
- Individual (k) — round to nearest
- Individual (k) — floor

Backup — Drug forgiveness: where does a missed dose actually hurt?



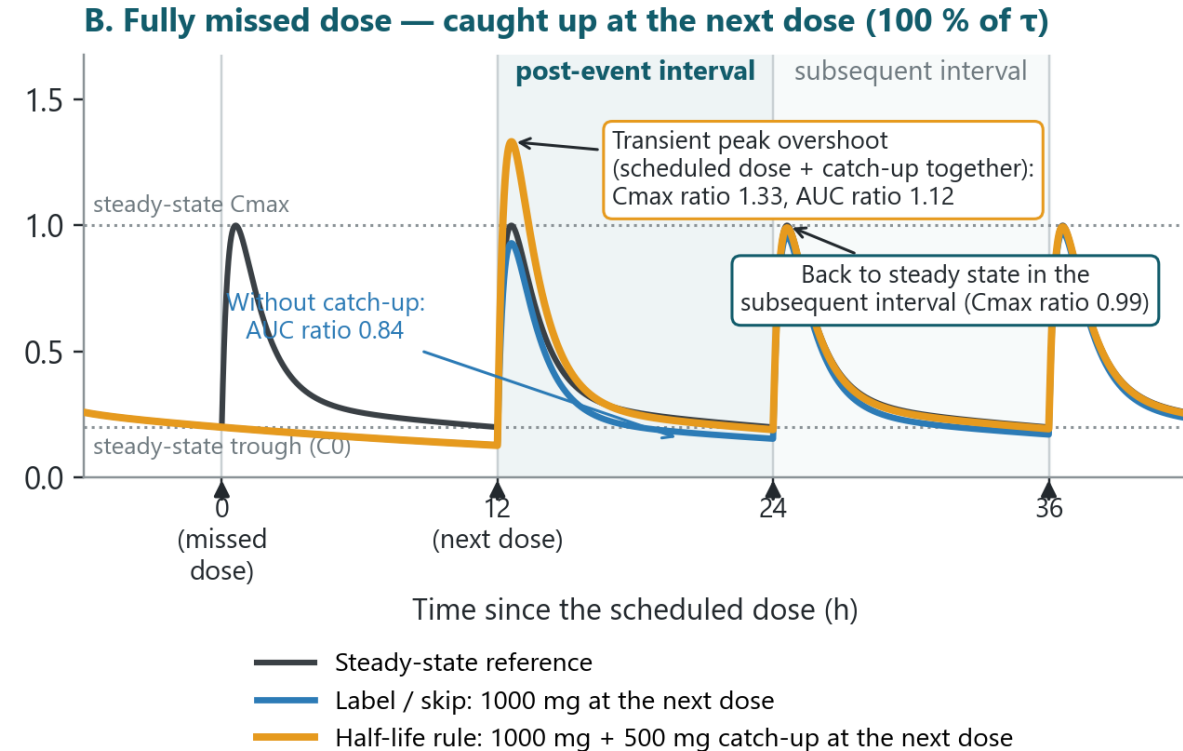
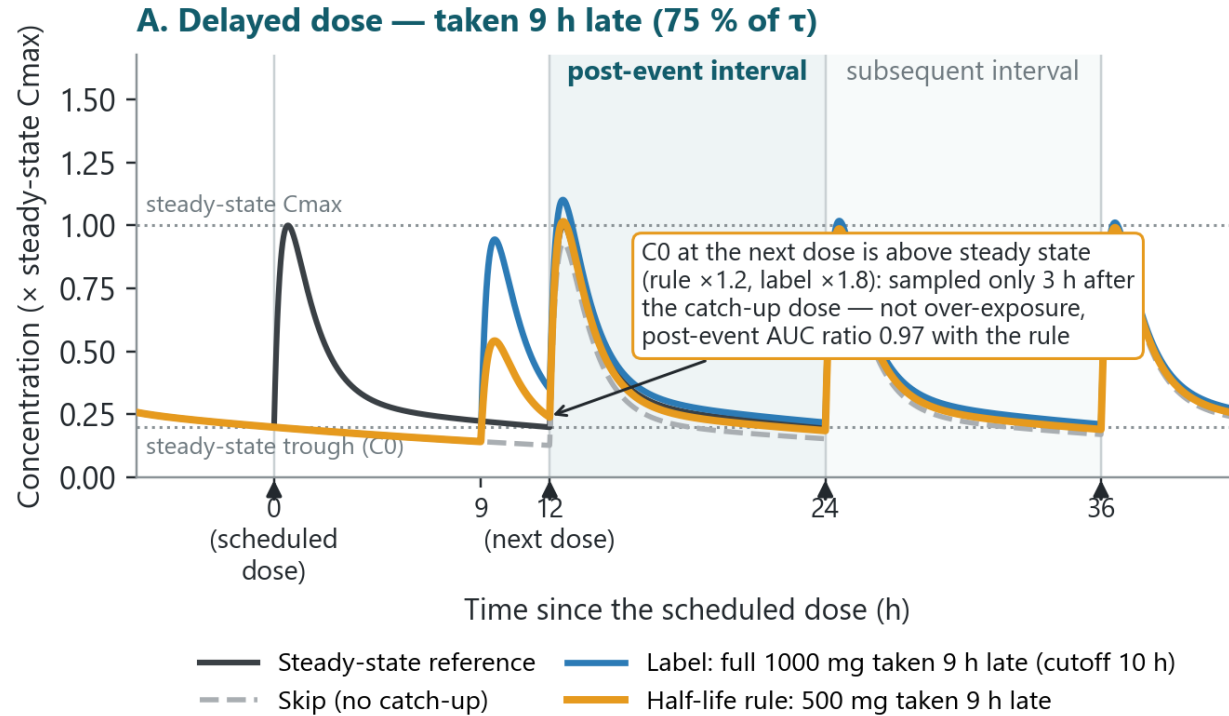
Worst when the effective $t_{1/2} \approx \tau$ — forgiveness must be measured by simulation, not read off the terminal half-life.

Backup — Table 1. Drug models and simulation settings

Drug / model	Standard regimen	Pop. $t_{1/2}$ (h)	τ (h)	$t_{1/2}/\tau$	Label cutoff	Label instruction (operationalized, eTable 1)
Amoxicillin	1000 mg TID	1.0	8	0.13	4 h	as soon as remembered, $\approx$ 4 h before the next dose
Levofloxacin	500 mg QD	7.0	24	0.29	16 h	only if $\geq$ 8 h remain before the next dose
Tacrolimus LCPT (Envarsus)	5 mg QD	11.7	24	0.49	15 h	as soon as possible within 15 h
Tacrolimus PR (Advagraf)	5 mg QD	15.6	24	0.65	14 h	up to 14 h after the scheduled time
Carvedilol	6.25 mg BID	8.0	12	0.67	6 h	no two doses within 6 h
Tacrolimus IR (Prograf)	5 mg BID	15.6	12	1.30	6 h	if $\leq$ 6 h late; never double
Mycophenolate mofetil	1000 mg BID	17.9	12	1.49	10 h	unless the next dose is $<$ 2 h away
Abemaciclib	150 mg BID	24.8	12	2.07	omit	never take an additional dose
Azithromycin	500 mg QD	68	24	2.83	12 h	if $\leq$ 12 h have elapsed
Hydroxychloroquine	400 mg QD	768	24	32.0	12 h	omit if the next dose is within 12 h
Amiodarone	400 mg QD	1392	24	58.0	none	“unless nearly time for the next dose” $\rightarrow$ omit

Sorted by $t_{1/2}/\tau$. Cutoffs operationalized from the most recent FDA / EMA product information. Simulations: R 4.4.2, mrgsolve 1.5.2, 1,000 virtual patients per model, $\geq$ 7 dosing intervals to steady state; delays 10/20/33/50/75/100 % of τ .

A higher trough or peak after a catch-up is expected — and transient



Trough sampled a few hours after the catch-up $\rightarrow$ higher, with AUC on target. **Peak overshoot** $\rightarrow$ only after a fully missed dose of rapid-absorption drugs, gone by the next interval.

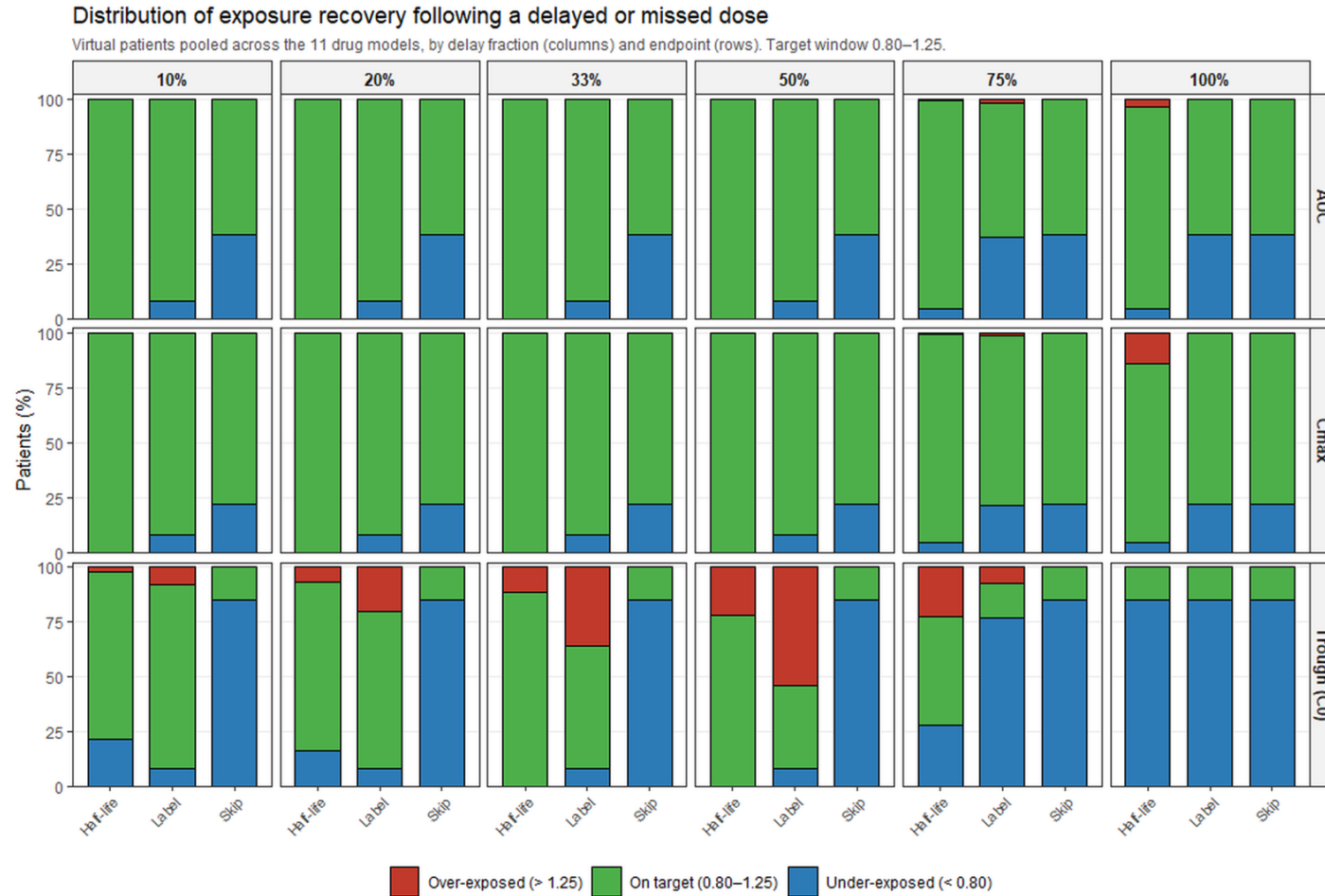
Illustrative 2-compartment simulation (mycophenolate-like); ratios vs steady state.

Backup — AUC target attainment by drug model and delay (% of patients)

Drug model	Rule 10 %	Rule 20 %	Rule 33 %	Rule 50 %	Rule 75 %	Rule 100 %	Label 10 %	Label 20 %	Label 33 %	Label 50 %	Label 75 %	Label 100 %	Skip
Amoxicillin	100	100	100	100	92	99	100	100	100	100	99	99	99
Levofloxacin	100	100	100	100	49	49	100	100	100	100	49	49	49
Tacrolimus LCPT	100	100	100	100	100	100	100	100	100	100	0	0	0
Tacrolimus PR	100	100	100	100	100	95	100	100	100	100	54	54	54
Carvedilol	100	100	100	100	100	100	100	100	100	100	100	100	100
Tacrolimus IR	100	100	100	100	100	98	100	100	100	100	52	52	52
Mycophenolate mofetil	100	100	100	100	100	77	100	100	100	99	76	85	85
Abemaciclib	100	100	100	100	100	100	12	12	12	12	12	12	12
Azithromycin	100	100	100	100	100	91	100	100	100	100	100	100	100
Hydroxychloroquine	100	100	100	100	100	100	100	100	100	100	26	26	26
Amiodarone	100	100	100	100	100	100	100	100	100	100	100	100	100
Mean (11 models)	100.0	100.0	100.0	100.0	94.6	91.8	92.0	92.0	92.0	91.9	60.8	61.6	61.6

Green ≥ 95 %, yellow 80–94 %, red < 80 % within 0.80–1.25 of steady-state AUC in the post-event interval (eTable 2). Skip is independent of the delay. Abemaciclib and amiodarone labels operationalize as omission at every delay.

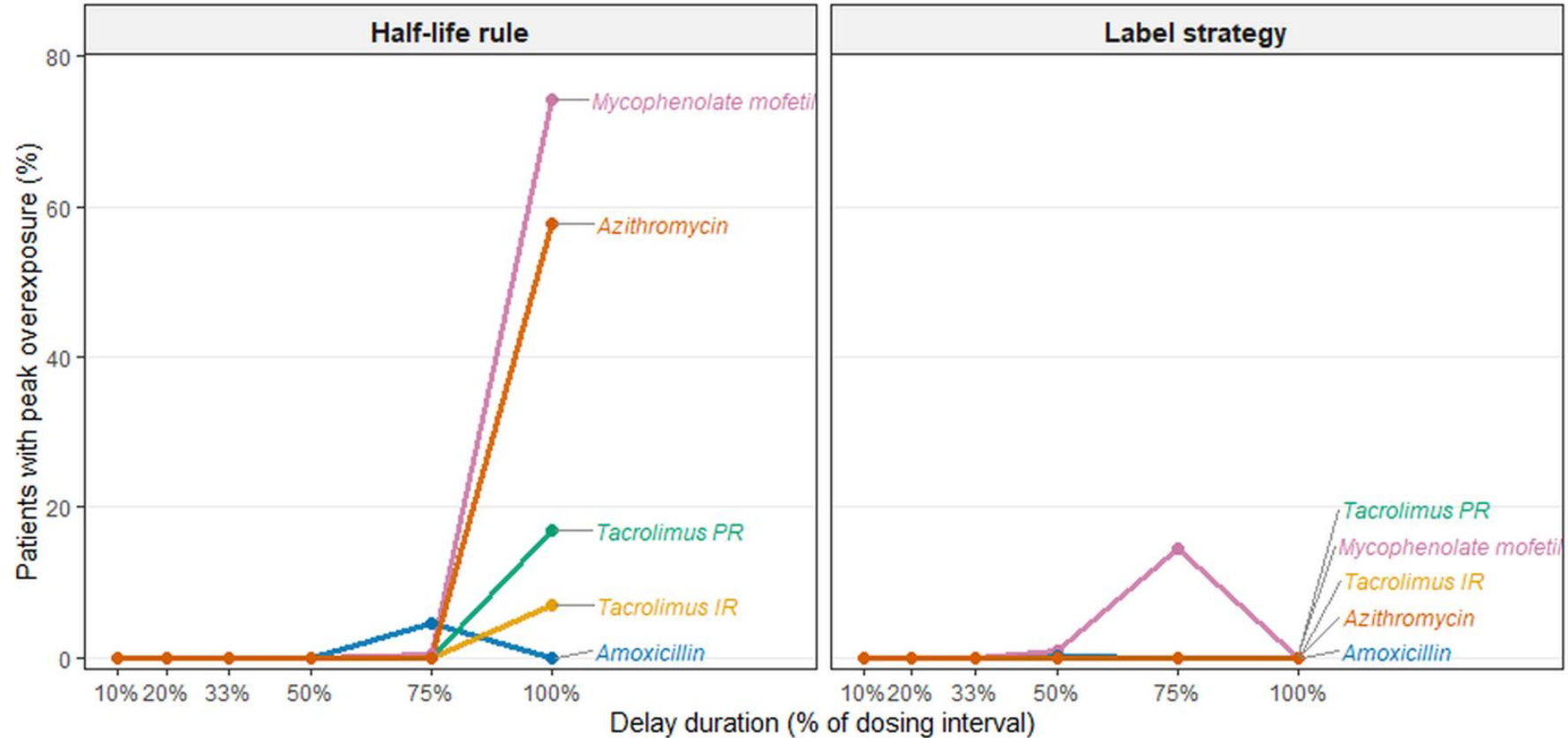
Backup — Figure 2. AUC, $C_{\max}$ and C_0 ratio distributions (pooled)



Backup — Figure 3. Heterogeneity of peak overexposure

Heterogeneity of peak overexposure across drug models

Percentage of virtual patients with C_{max} ratio > 1.25 in the post-event interval. Only the 5 of 11 models with at least one overexposed patient are shown



Backup — levofloxacin 500 mg QD: rule output by delay

$t_{1/2}$ 7 h · τ 24 h · label cutoff 16 h · strengths 250 and 500 mg (250-mg steps)

Delay	max(M, S)	Exact dose	Rule gives	Label gives
2.4 h (10 %)	0.97	486 mg	250 mg	500 mg
4.8 h (20 %)	0.94	469 mg	250 mg	500 mg
7.9 h (33 %)	0.88	439 mg	250 mg	500 mg
12 h (50 %)	0.77	383 mg	250 mg	500 mg
18 h (75 %)	0.49	247 mg	omit	omit
24 h (100 %)	0.09	46 mg	omit	omit

- At 18 h the exact dose (247 mg) rounds down below the 250-mg tablet → omission, like the label; median AUC ratio 0.80.
- Floor rounding avoids the overshoot of round-to-nearest; individual k_e adds little over the population $t_{1/2}$ (Fig. 4B).



Backup — tacrolimus IR: finer strengths, finer catch-up

5 mg BID · $t_{1/2}$ 15.6 h · label cutoff 6 h · capsules 0.5 / 1 / 5 mg

Delay	max(M, S)	Exact dose	0.5-mg steps	Full / half / none	Label gives
1.2 h (10 %)	0.95	4.74 mg	4.5 mg	2.5 mg	5 mg
2.4 h (20 %)	0.90	4.49 mg	4.0 mg	2.5 mg	5 mg
4 h (33 %)	0.84	4.19 mg	4.0 mg	2.5 mg	5 mg
6 h (50 %)	0.77	3.83 mg	3.5 mg	2.5 mg	5 mg
9 h (75 %)	0.67	3.35 mg	3.0 mg	2.5 mg	omit
12 h (100 %)	0.59	2.93 mg	2.5 mg	2.5 mg	omit

- With 0.5-mg capsules the catch-up tracks the exact dose within 0.5 mg; “full / half / none” floors to 2.5 mg at every delay → systematic under-compensation.
- Fully missed dose: 2.5 mg added to the scheduled 5 mg → AUC on target in 98 %, $C_{\max}$ ratio > 1.25 in 7 %, nothing persisting.
- Beyond the 6-h cutoff the label skips → 52 % on target only.

Tacrolimus IR — patients on target (%)

