

Bedaquiline paediatric daily dosing guidance

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4. BEDAQUILINE PAEDIATRIC DAILY DOSING GUIDANCE

Bedaquiline dosing for children and adolescents is based on age and weight; bedaquiline should be administered **daily throughout the treatment period** as follows:

- **Weeks 1–2:** Loading dose daily for 2 weeks
- **Weeks 3–24:** Thereafter daily dose for 22 weeks

Table 2: Bedaquiline <u>Paediatric</u> Dosing							
Age	0 to <3 months	3 to <6 months	≥ 6 months				
Weight	All	All	3-<7kg	7-<10kg	10-<16kg	16-<30kg	≥30kg
Week 1-2	30mg daily	60mg daily	60mg daily	80mg daily	120mg daily	200mg daily	400mg daily
Week 3-24	5mg daily	10mg daily	10mg daily	20mg daily	30mg daily	50mg daily	100mg daily

Bedaquiline is available in 20mg dispersible tablets (paediatric formulation) as well as 100mg scored tablets (adult formulation) which may be crushed and mixed with water for more accurate administration of paediatric doses.



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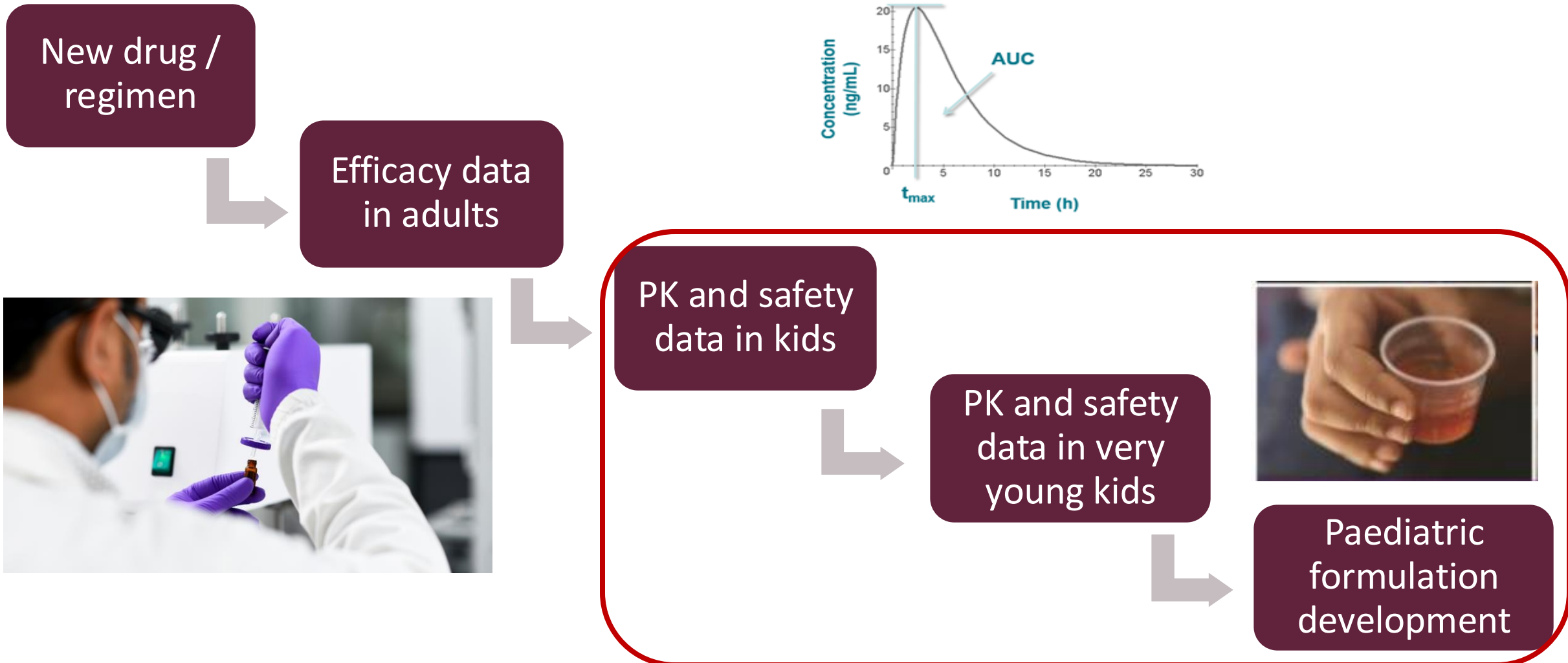
8. PAEDIATRIC RELOADING AFTER BEDAQUILINE (BDQ) INTERRUPTION

If the initial loading period is interrupted, complete a total of 14 loading doses before changing to maintenance dosing. Do not double missed doses.

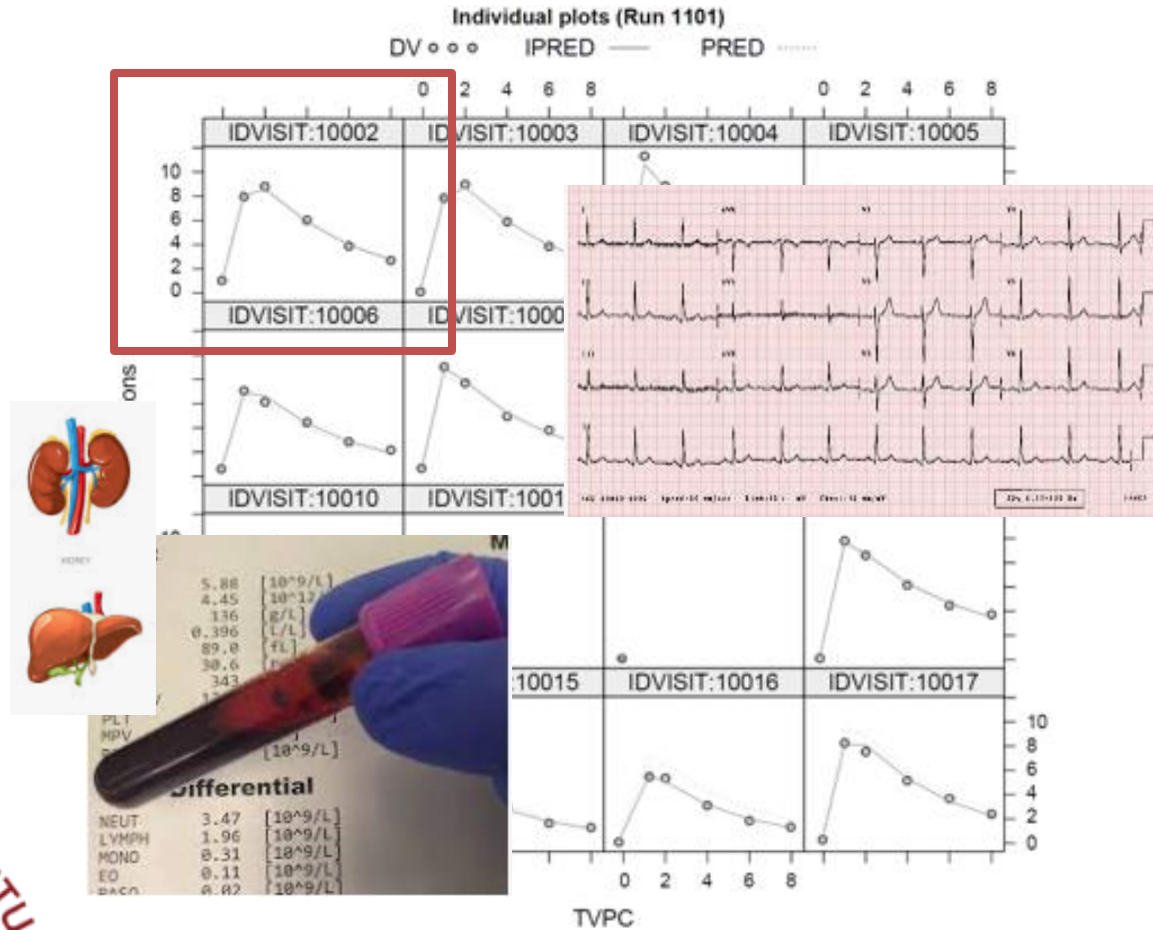
For children or adolescents who interrupt treatment after the initial 2-week loading phase, refer to the paediatric dosing table above and reload as follows:

- <1 week interruption: no bedaquiline reloading (i.e., immediately resume daily maintenance dose per the paediatric dosing table above)
- 1-4 weeks interruption: reload with 3 days of bedaquiline age- and weight-appropriate loading dose, followed by daily maintenance dose
- ≥ 4 weeks interruption: reload with 7 days of bedaquiline age- and weight-appropriate loading dose, followed by daily maintenance dose.
- *Only following a period of **more than one year without bedaquiline**, should a full 14-day reload with the age- and weight-appropriate loading dose be considered before resuming maintenance dosing.*

How to achieve the goal for children



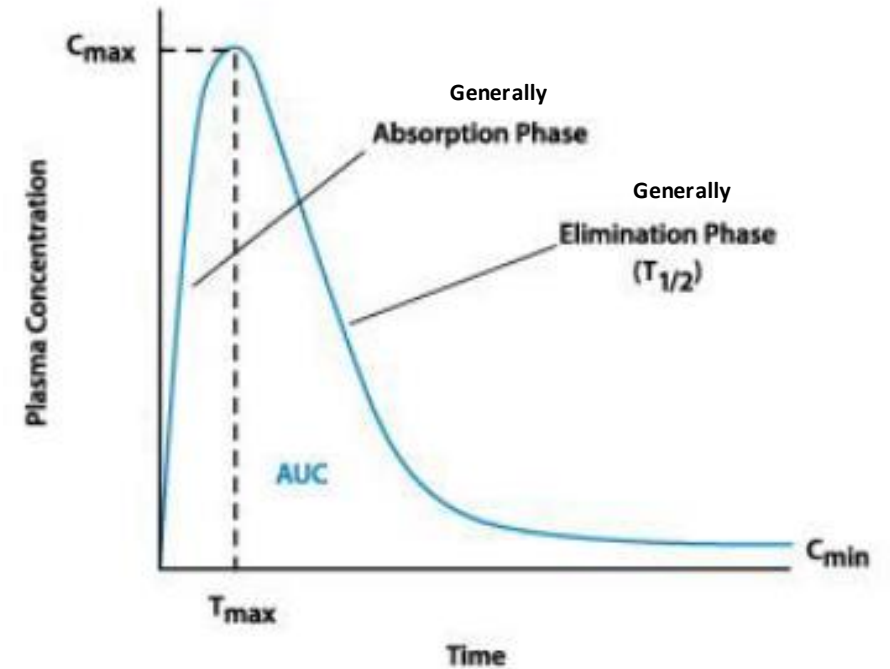
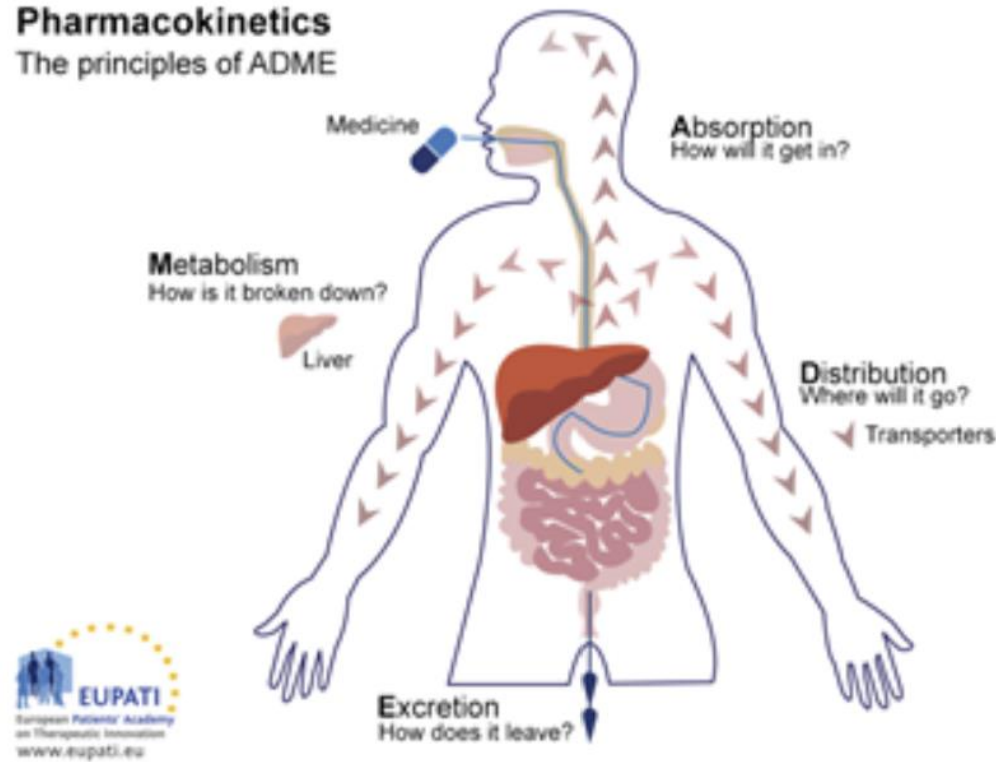
Pharmacokinetic studies



(L) ADME - PK

Pharmacokinetics

The principles of ADME



<https://learning.eupati.eu/mod/book/view.php?id=357&chapterid=351>, and figure courtesy of Paolo Denti

Bedaquiline PK key features

- Bioavailability increased two-fold with food
- Extremely long terminal half-life, >5 months
- Metabolized by CYP3A4 to M2, same path for M2
- Bedaquiline and M2 >99.9% and >99.7% protein bound
- PK-PD:
 - Average bedaquiline concentrations linked to rate of bacterial clearance
 - M2 linked to QT prolongation

Report of a WHO expert consultation on dosing to enable implementation of treatment recommendations in the WHO consolidated guidelines on the management of TB in children and adolescents. Geneva: World Health Organization; 2022. Licence: CC BY-NC-SA 3.0 IGO.
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Liu et al. Drug Metab Dispos. 2014;42(5):863-6. Svensson et al. J Antimicrob Chemother. 2017;72(12):3398-405.

Steady state

At steady state!

$$AUC = \frac{Dose \cdot F}{CL}$$

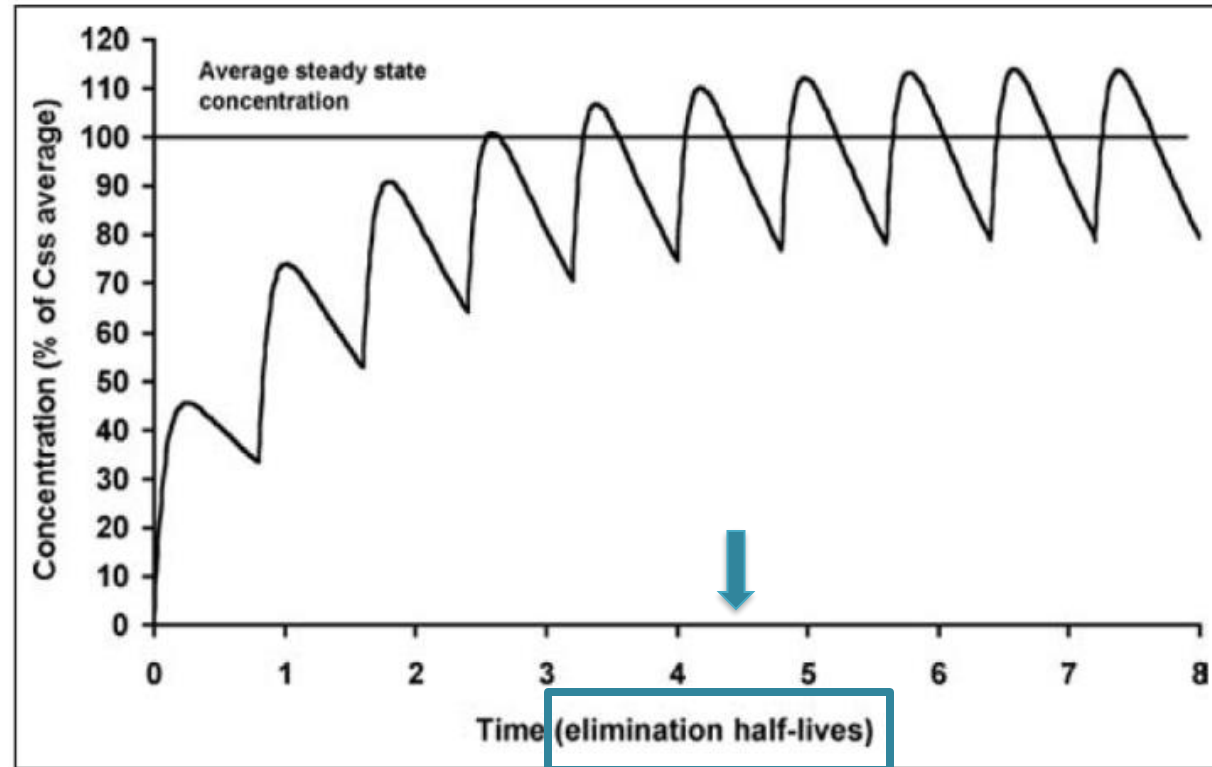
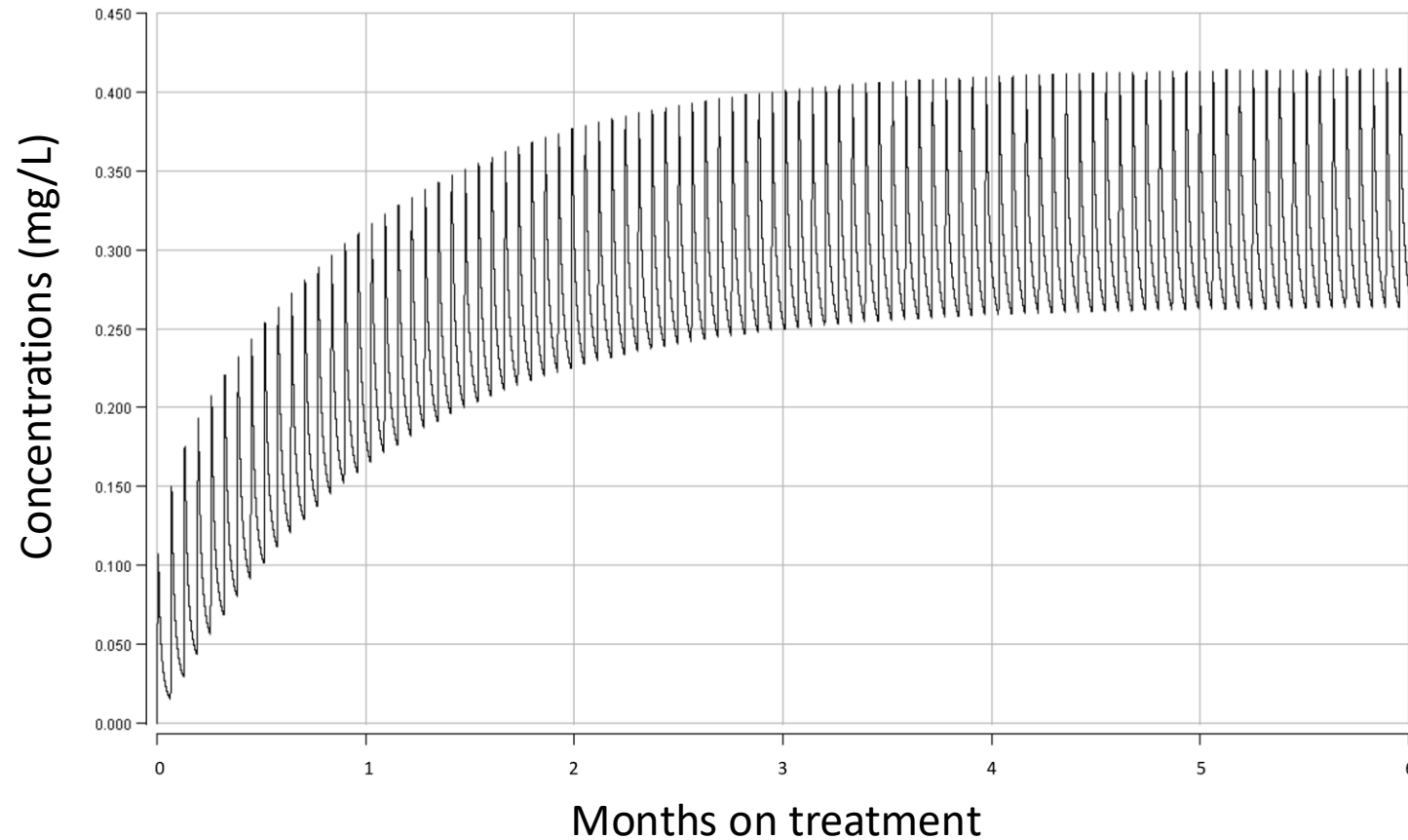


Figure 2: Concentration-time profile for a drug given as a regular maintenance oral dose

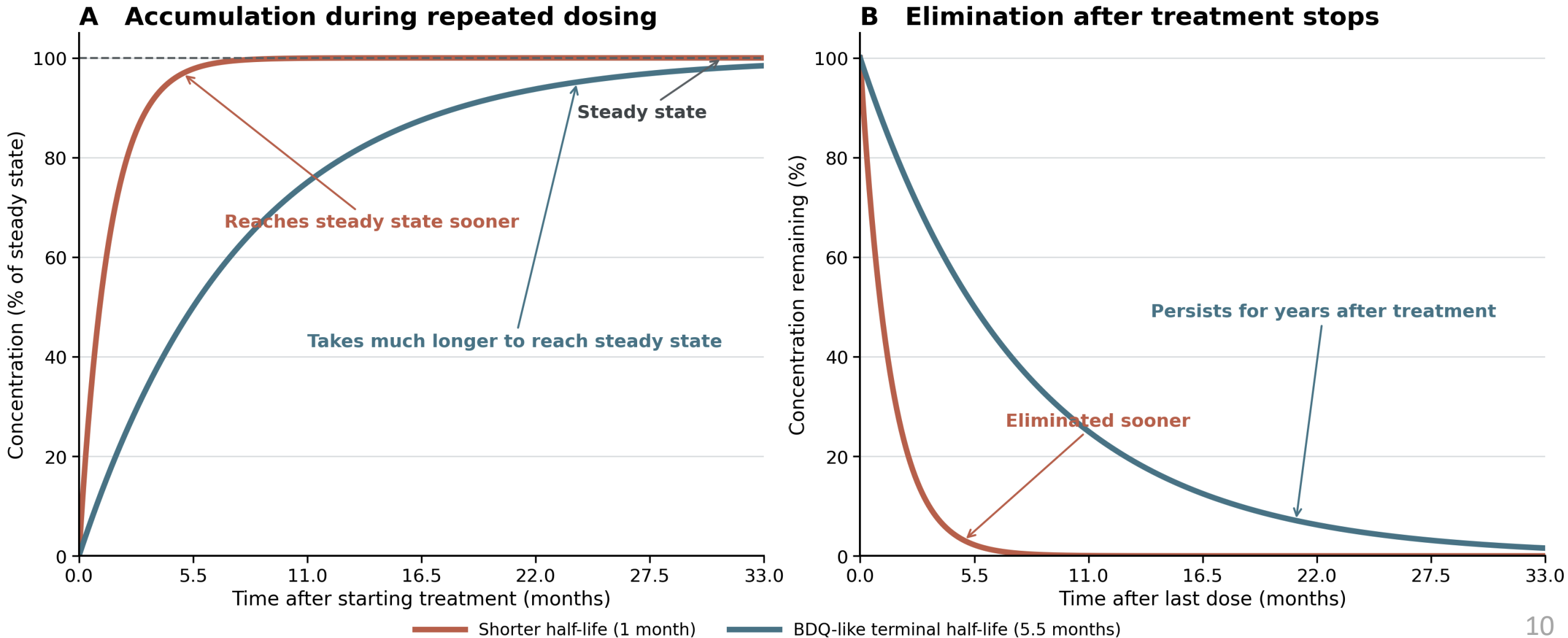
<https://pharmaceutical-journal.com/article/ld/back-to-basics-pharmacokinetics>

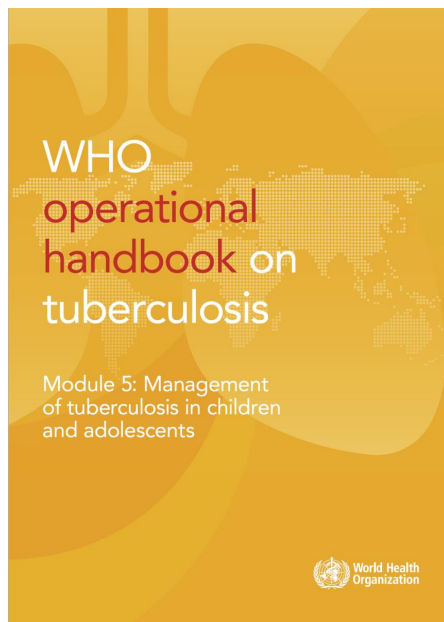
Half life, steady state, AUC



Steady state and washout (~4-5 half-lives)

Very long half-life: slow accumulation and prolonged washout





Group	Medicine	Weight-based daily dose ^b	Formulations (mg/mL, as applicable)	Weight bands ^a								Usual upper daily dose ^b	Comments
				3 to <5 kg	5 to <7 kg	7 to <10 kg	10 to <16 kg	16 to <24 kg	24 to <30 kg	30 to <36 kg	36 to <46 kg		
A	Levofloxacin	15–20 mg/kg	100 mg dt	5 mL (0.5 dt)	1	1.5	2	3	-	-	-	1.5 g	
			250 mg tab (250 mg in 10 mL = 25 mg/mL)	2 mL ^c	5 mL (0.5 tab) ^c	5 mL (0.5 tab) ^c	1	1.5	2	3	3	1.5 g	
	Moxifloxacin	10–15 mg/kg (standard dose) ^d	100 mg dt (100 mg in 10 mL = 10 mg/mL)	4 mL	8 mL	1.5	2	3	4	4	4	400 mg	
			400 mg tab (400 mg in 10 mL = 40 mg/mL)	1 mL ^c	2 mL ^c	3 mL ^c	5 mL ^c (0.5 tab)	7.5 mL ^c (0.75 tab)	1	1	1	400 mg	
			High dose ^d	400 mg tab	-	-	-	-	-	1 or 1.5	1.5	800 mg	
	Bedaquiline	-	20 mg dt ^e	0 to <3 months: 1.5 od for 2 weeks; then 0.5 od M/W/F for 22 weeks	0 to <3 months: 1.5 od for 2 weeks; then 0.5 od M/W/F for 22 weeks	3 to <6 months: 3 od for 2 weeks; then 1 od M/W/F for 22 weeks	3 to <6 months: 3 od for 2 weeks; then 1 od M/W/F for 22 weeks	10 od for 2 weeks; then 5 od M/W/F for 22 weeks	20 od for 2 weeks; then 10 od M/W/F for 22 weeks	-	-	-	
				≥ 3 months: 3 od for 2 weeks; then 1 od M/W/F for 22 weeks	3 to <6 months: 3 od for 2 weeks; then 1 od M/W/F for 22 weeks	≥ 6 months: 4 od for 2 weeks; then 2 od M/W/F for 22 weeks	≥ 6 months: 4 od for 2 weeks; then 2 od M/W/F for 22 weeks	-	-	-	-	-	
		-	100 mg tab ^e	0 to <3 months: 3 mL od for 2 weeks; then 1 mL od M/W/F for 22 weeks ^c	0 to <3 months: 3 mL od for 2 weeks; then 1 mL od M/W/F for 22 weeks ^c	3 to <6 months: 6 mL od for 2 weeks; then 2 mL od M/W/F for 22 weeks ^c	3 to <6 months: 6 mL od for 2 weeks; then 2 mL od M/W/F for 22 weeks ^c	2 od for 2 weeks; then 1 od M/W/F for 22 weeks	4 od for 2 weeks; then 2 od M/W/F for 22 weeks	-	-	-	A daily loading dose is used for the first 2 weeks, followed by a maintenance dose given three times a week
				≥ 3 months: 6 mL od for 2 weeks; then 2 mL od M/W/F for 22 weeks ^c	3 to <6 months: 6 mL od for 2 weeks; then 2 mL od M/W/F for 22 weeks ^c	≥ 6 months: 8 mL od for 2 weeks; then 4 mL od M/W/F for 22 weeks ^c	≥ 6 months: 8 mL od for 2 weeks; then 4 mL od M/W/F for 22 weeks ^c	-	-	-	-	-	

Loading doses

BDQ dosing remains complex

Current loading and maintenance schedules

CHILDREN WHO weight bands

Most regimens

2-WEEK LOADING

weight-band dose daily

MAINTENANCE M W F

weight-band dose

ADULTS Labelled schedule

Other regimens

2-WEEK LOADING

400 mg daily

MAINTENANCE M W F

200 mg

ADULTS / ADOLESCENTS ZeNix option

BPaL / BPaLM

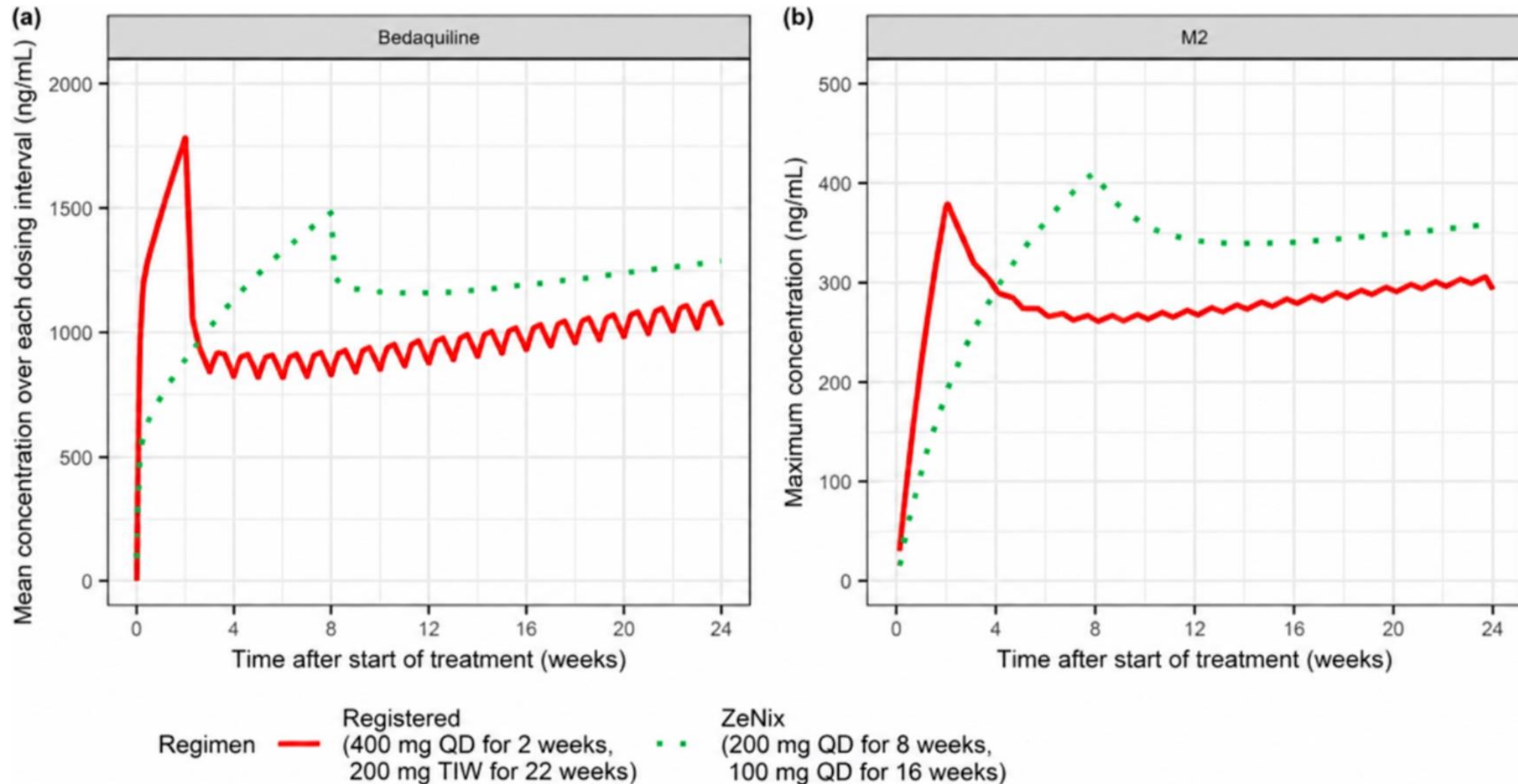
2-MONTH LOADING

200 mg daily

DAILY MAINTENANCE

100 mg daily

BDQ dosing remains complex – different reloading



BDQ reloading based on dosing schedule

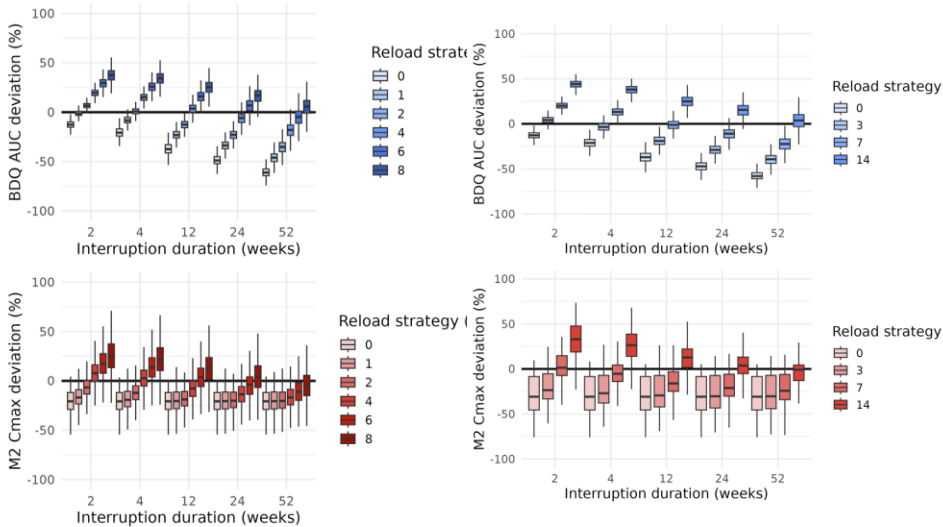
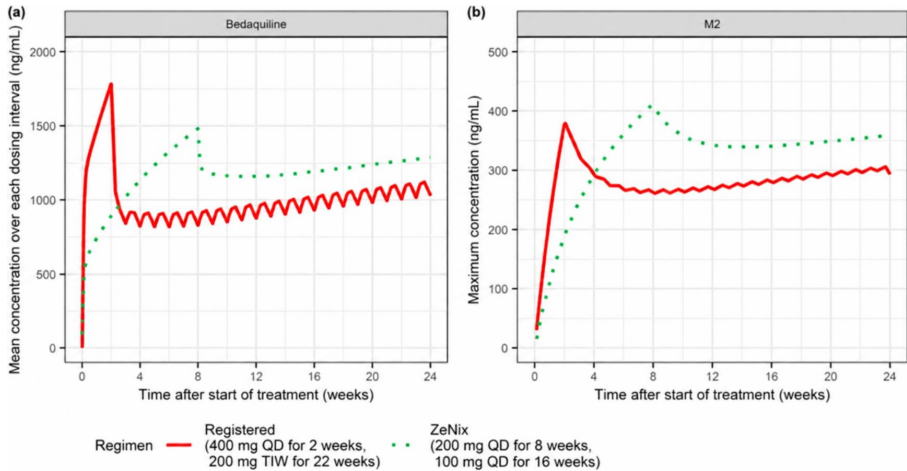
Bedaquiline reloading strategies following interruptions during daily dosing

Nienke Kikstra,^{1,2} Stijn W. van Beek,³ Gary Maartens,^{4,5} James C. M. Brust,⁶ Elin M. Svensson,^{1,7} Simon E. Koele¹

Also, no guidance yet if 2 Months loading interrupted!

TABLE 1 Optimized bedaquiline reloading strategies following interruptions of once-daily 100 mg bedaquiline regimens

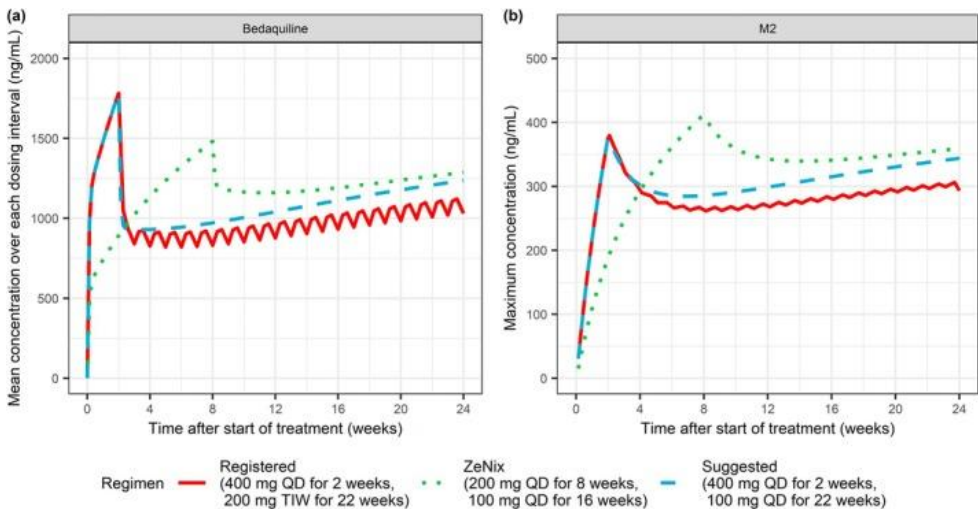
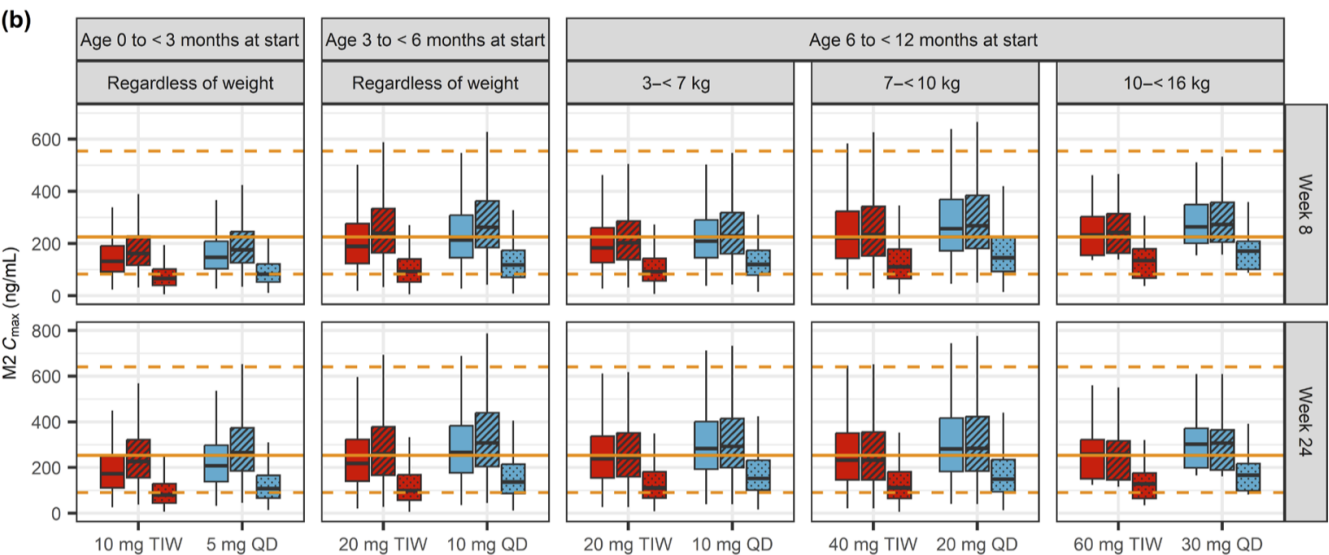
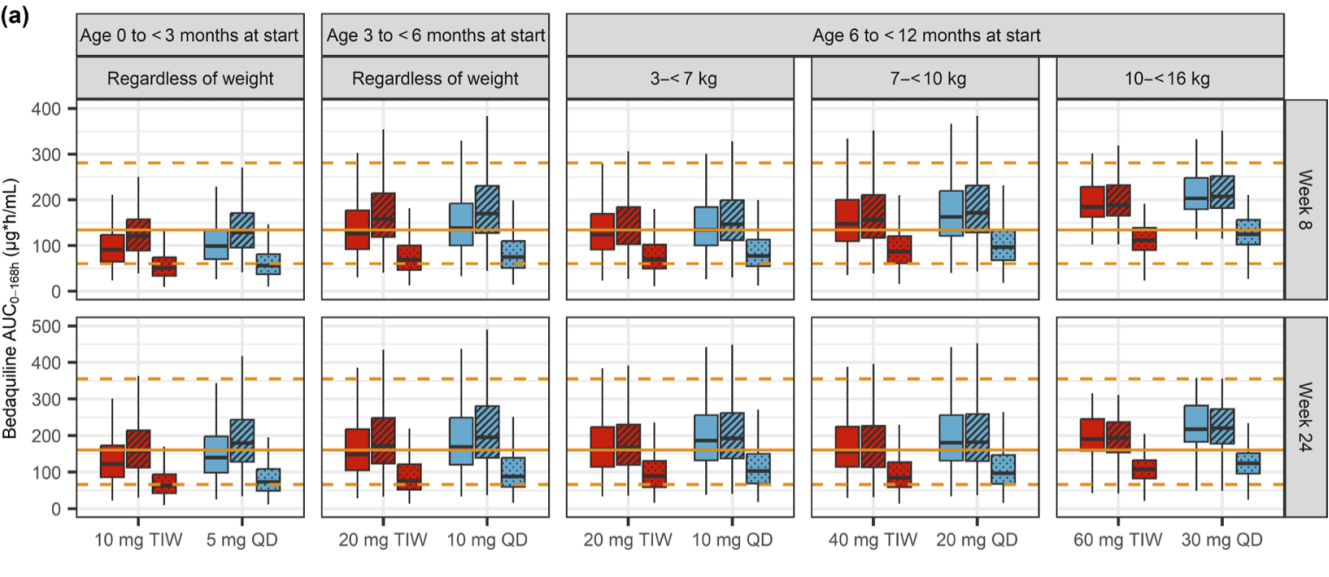
Interruption duration	Optimized reloading strategy
Daily dosing regimen starting with 8 weeks of loading	
<1 week	No reloading
1–3 weeks	1 week 200 mg bedaquiline daily
3–8 weeks	2 weeks 200 mg bedaquiline daily
8–18 weeks	4 weeks 200 mg bedaquiline daily
18–52 weeks	6 weeks 200 mg bedaquiline daily
≥52 weeks	8 weeks 200 mg bedaquiline daily
Daily dosing regimen starting with 2 weeks of loading	
<1 week	No reloading
1–4 weeks	3 days 400 mg bedaquiline daily
4–26 weeks	7 days 400 mg bedaquiline daily
≥26 weeks	14 days 400 mg bedaquiline daily



BDQ daily dosing

Model-Informed Once-Daily Dosing Strategy for Bedaquiline and Delamanid in Children, Adolescents and Adults with Tuberculosis

Yu-Jou Lin¹, Louvina E van der Laan², Mats O Karlsson¹, Anthony J Garcia-Prats^{2,3}, Anneke C Hesselting², Elin M Svensson^{1,4}

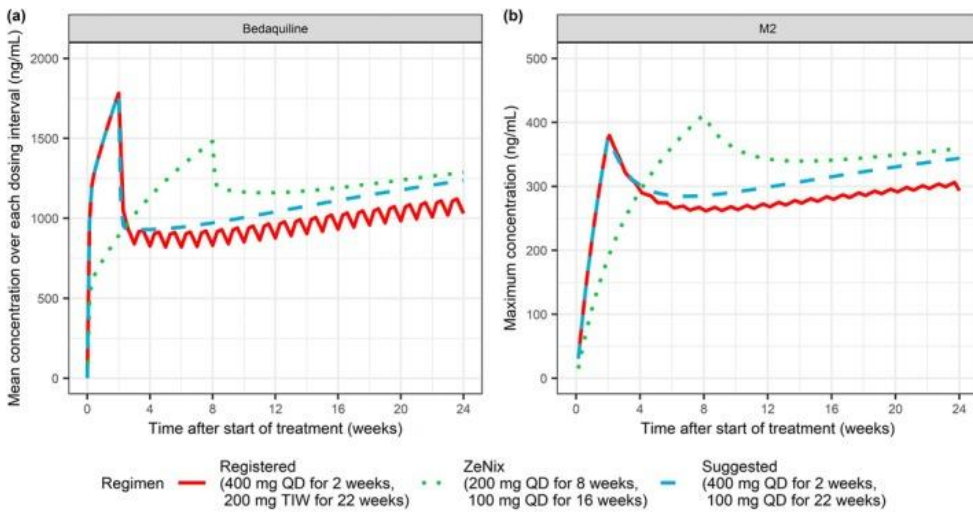
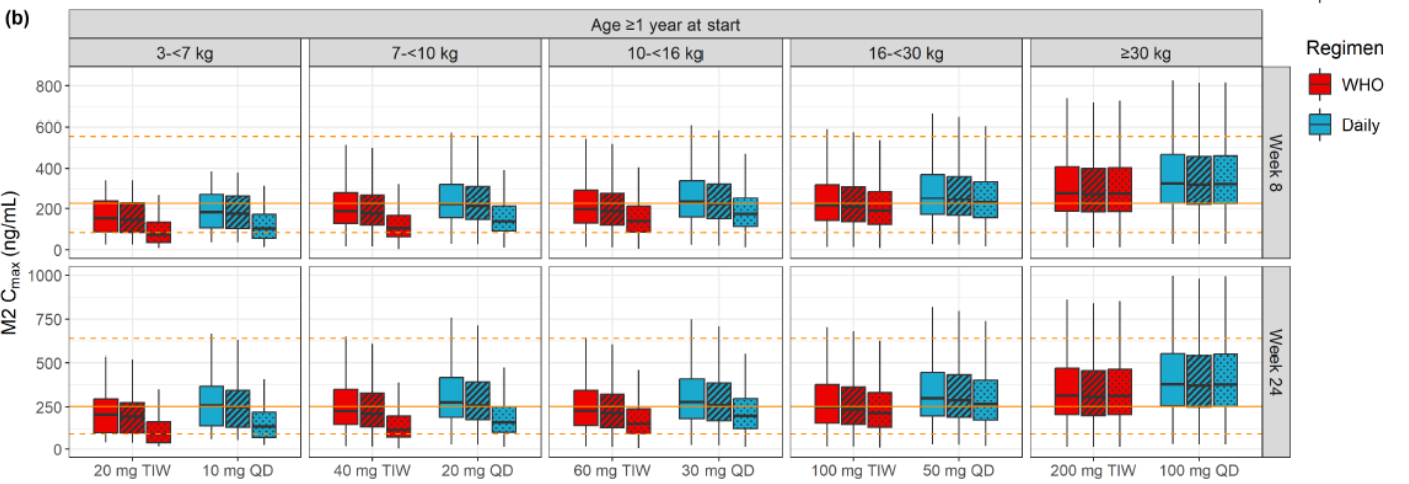
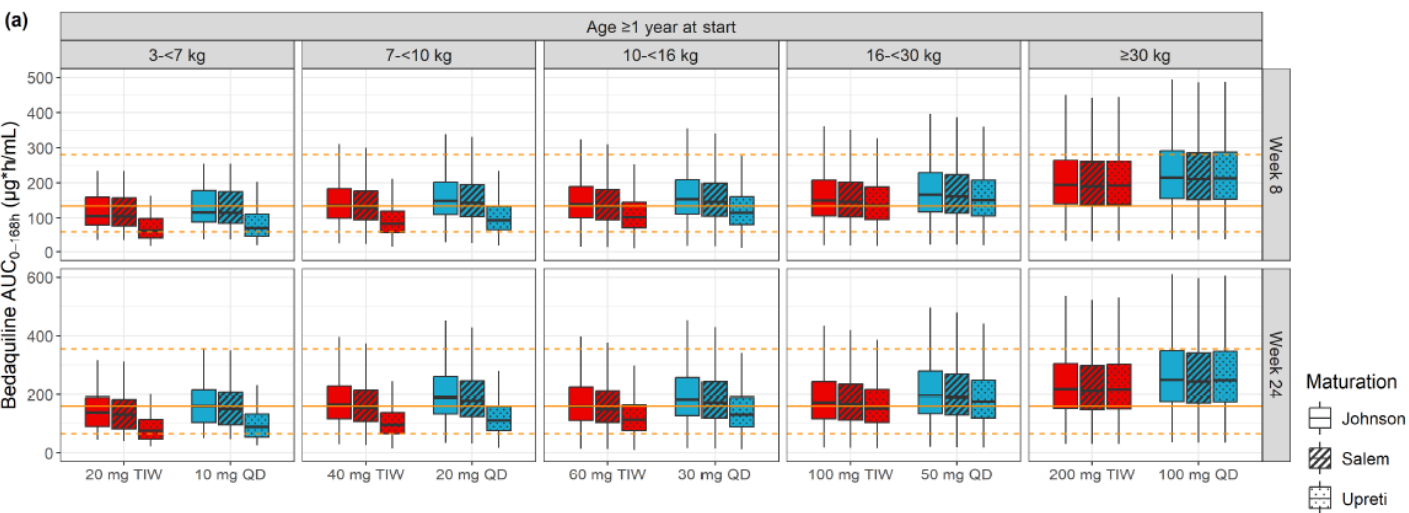


Bedaquiline			
Age	Weight	WHO dosing ^a	Daily dosing ^a
0 to < 3 months	All	30 mg QD/ 10 mg TIW	30 mg QD/ 5 mg QD
3 to < 6 months	All	60 mg QD/ 20 mg TIW	60 mg QD/ 10 mg QD
≥ 6 months	3 to < 7 kg	60 mg QD/ 20 mg TIW	60 mg QD/ 10 mg QD
	7 to < 10 kg	80 mg QD/ 40 mg TIW	80 mg QD/ 20 mg QD
	10 to < 16 kg	120 mg QD/ 60 mg TIW	120 mg QD/ 30 mg QD
	16 to < 30 kg	200 mg QD/ 100 mg TIW	200 mg QD/ 50 mg QD
	≥ 30 kg	400 mg QD/ 200 mg TIW	400 mg QD/ 100 mg QD

BDQ daily dosing

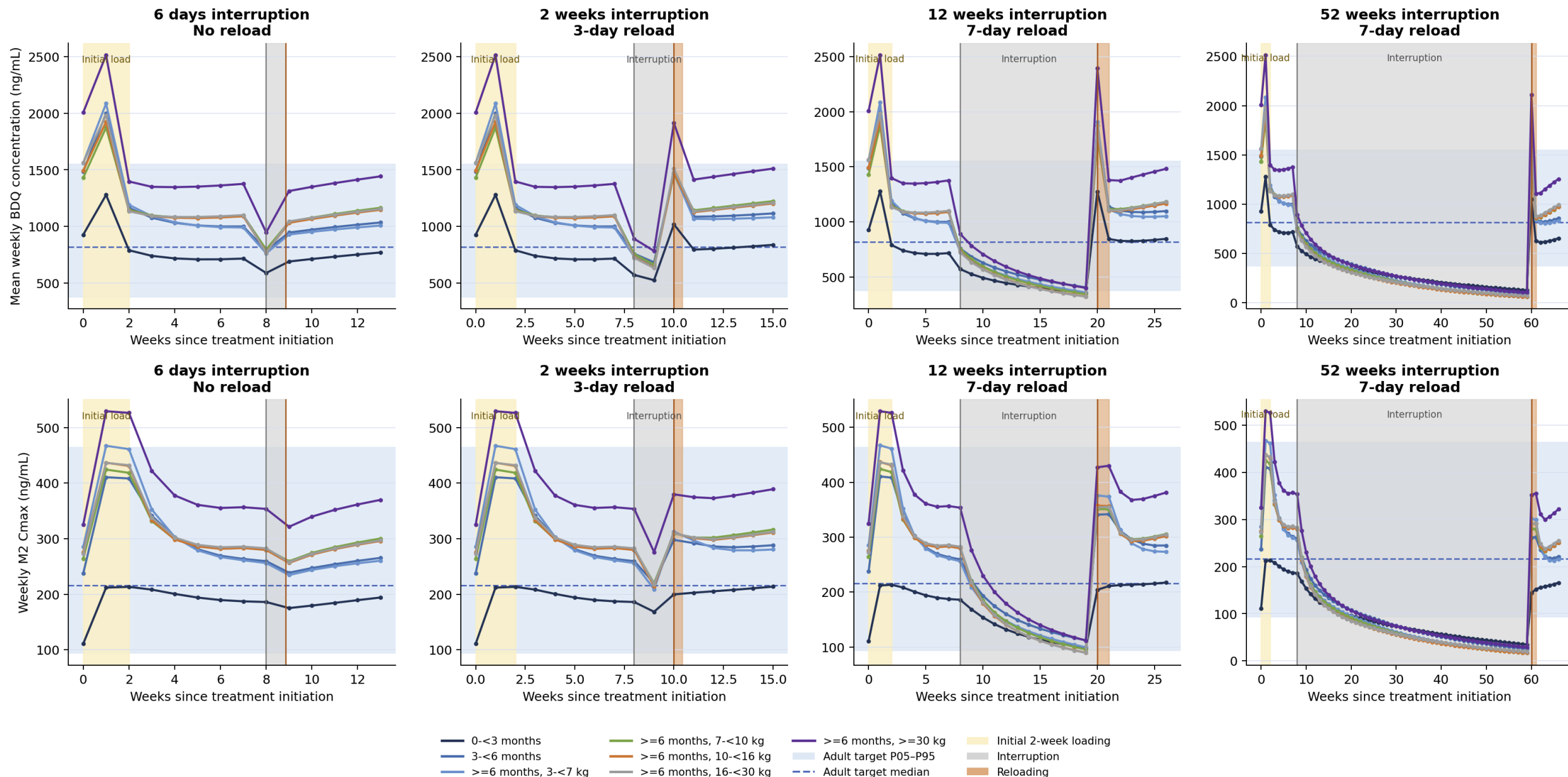
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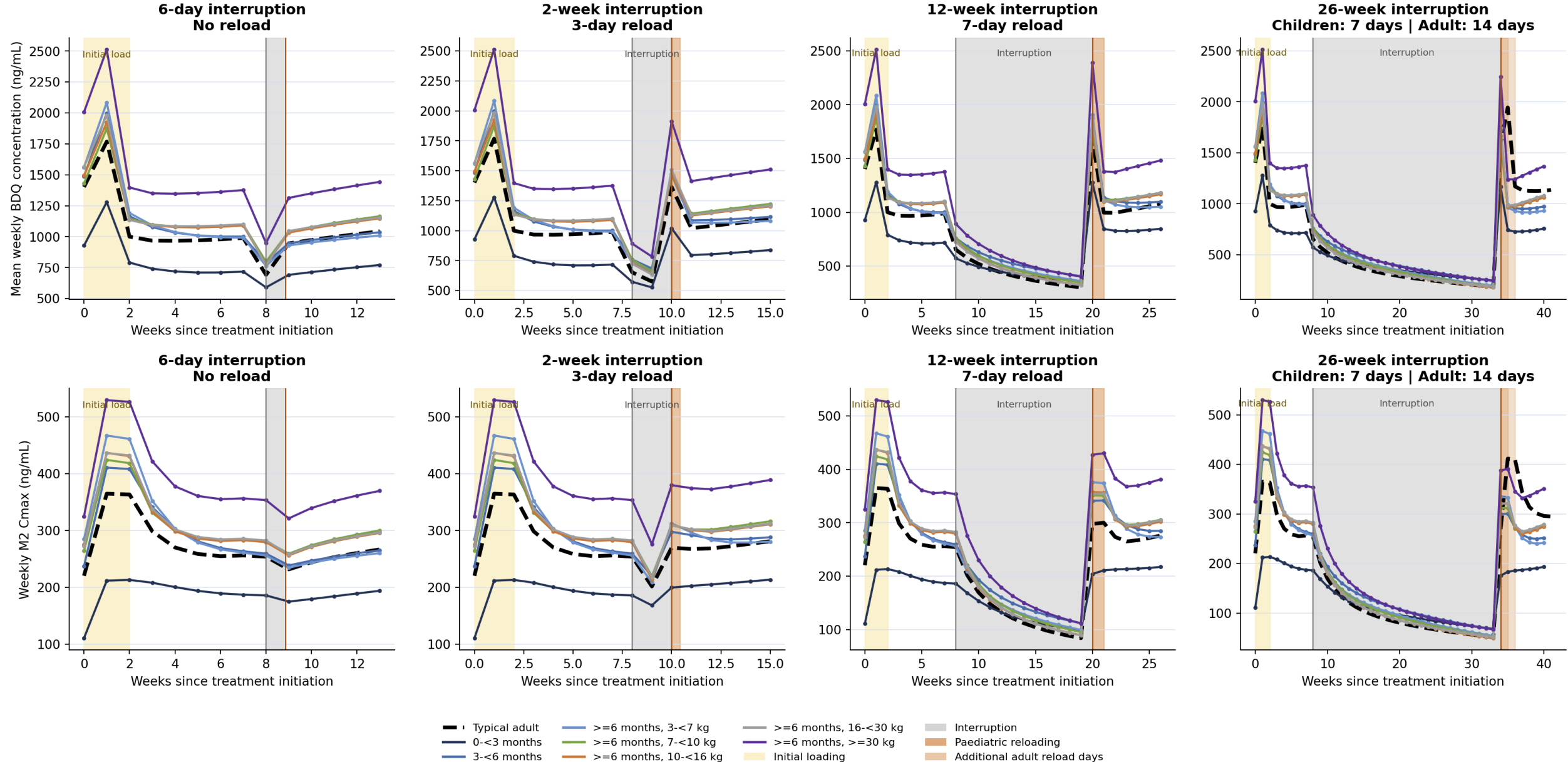
Bedaquiline			
Age	Weight	WHO dosing ^a	Daily dosing ^a
0 to <3 months	All	30 mg QD/ 10 mg TIW	30 mg QD/ 5 mg QD
3 to <6 months	All	60 mg QD/ 20 mg TIW	60 mg QD/ 10 mg QD
≥6 months	3 to <7 kg	60 mg QD/ 20 mg TIW	60 mg QD/ 10 mg QD
	7 to <10 kg	80 mg QD/ 40 mg TIW	80 mg QD/ 20 mg QD
	10 to <16 kg	120 mg QD/ 60 mg TIW	120 mg QD/ 30 mg QD
	16 to <30 kg	200 mg QD/ 100 mg TIW	200 mg QD/ 50 mg QD
	≥30 kg	400 mg QD/ 200 mg TIW	400 mg QD/ 100 mg QD

Paediatric BDQ reloading: simplified strategy (<1 week none; 1-4 weeks 3 days; >4 weeks 7 days)



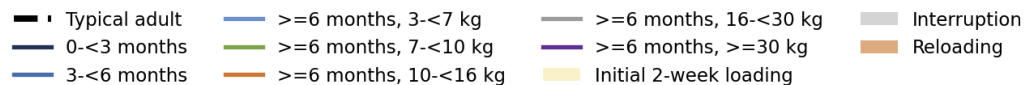
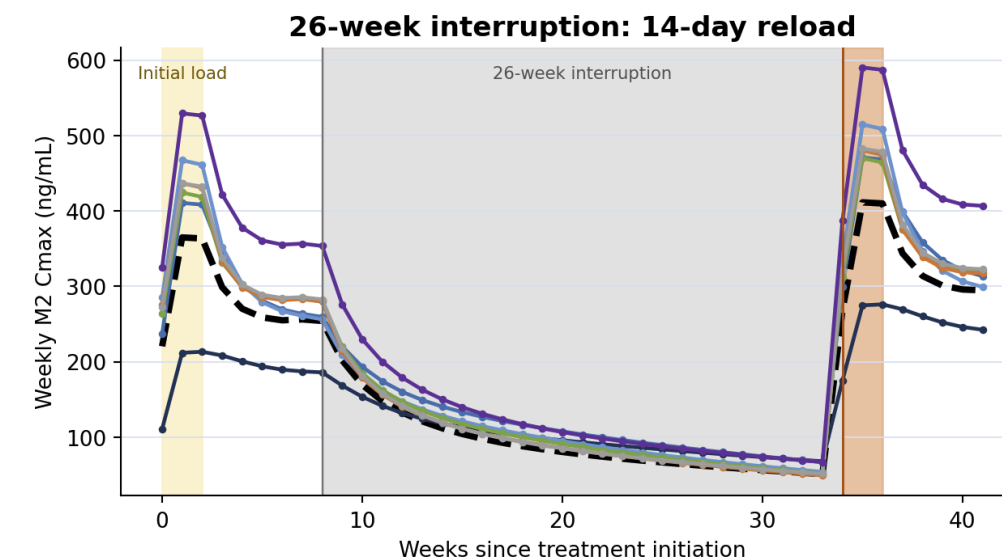
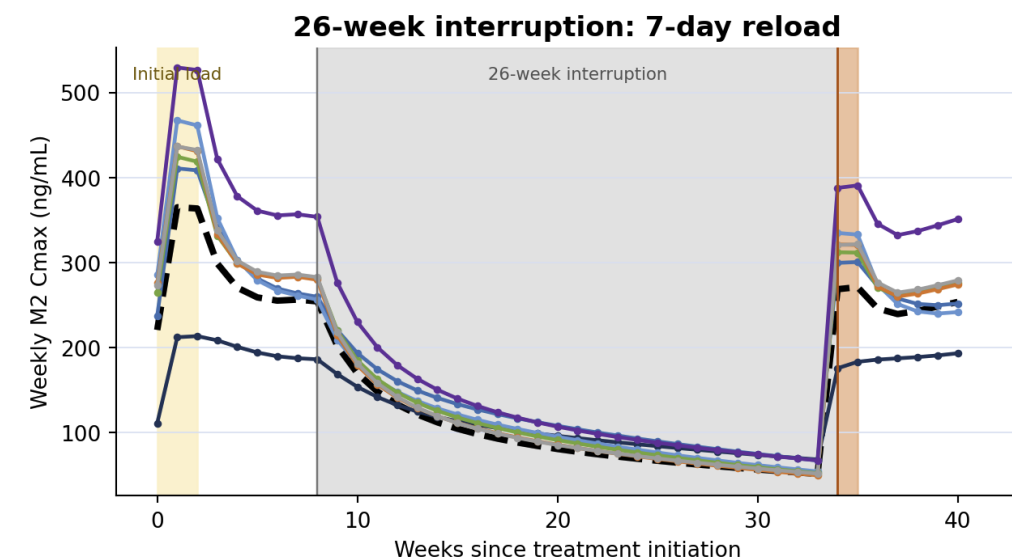
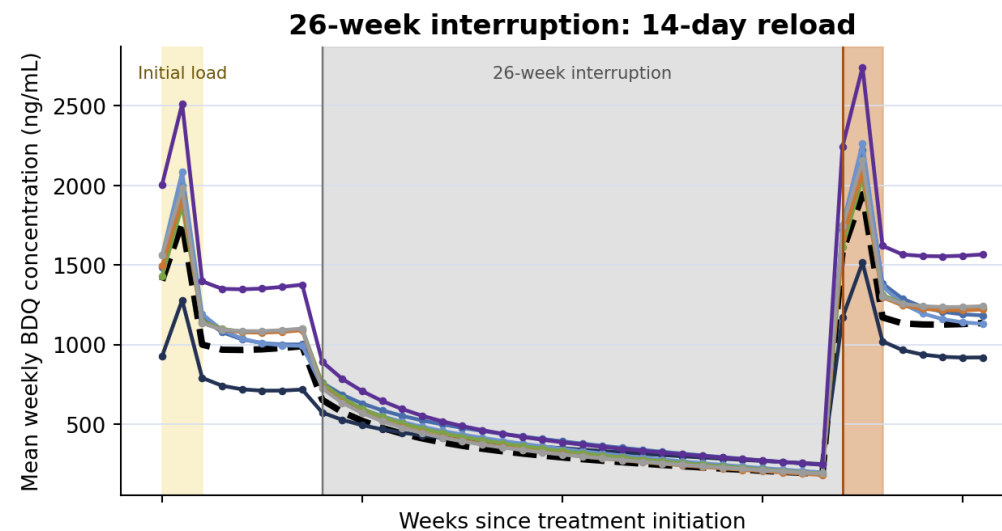
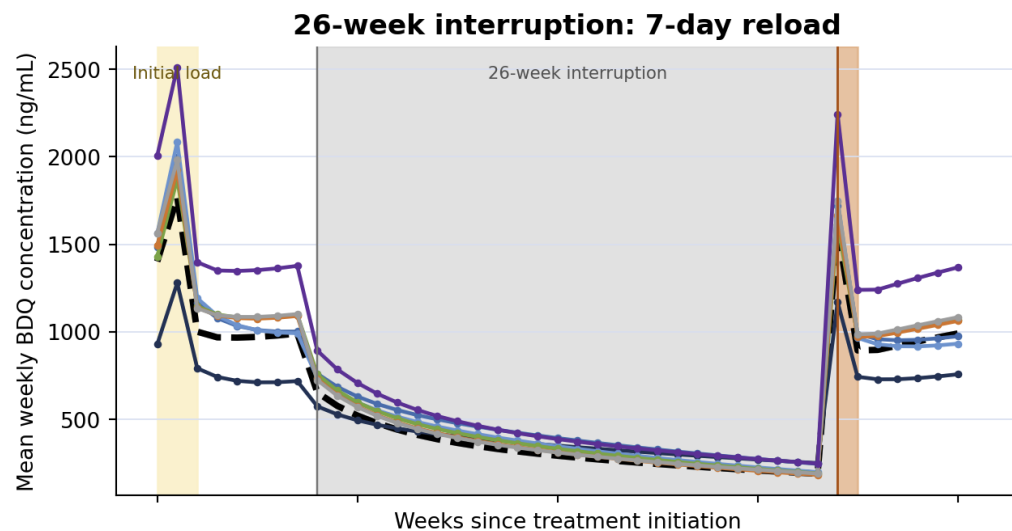
Typical age-weight profile for each paediatric dose band; Johnson CYP3A4 maturation model. Interruption begins after 8 weeks of treatment.

Model-informed paediatric bedaquiline reloading after completion of the initial 2-week load



Proposed paediatric strategy: <1 week, no reload; 1-4 weeks, 3 days; >4 weeks, 7 days. The final panel overlays the adult ≥26-week 14-day strategy.

Adult and paediatric BDQ/M2 exposure after a 26-week interruption



Interruption begins after 8 weeks of treatment. Lines show typical profiles without interindividual variability; paediatric profiles use the Johnson CYP3A4 maturation function.

Paediatric ratios:

Group	Loading/maintenance	Ratio
0–<3 months	30/5 mg	6:1
3–<6 months	60/10 mg	6:1
≥6 months, 3–<7 kg	60/10 mg	6:1
≥6 months, 7–<10 kg	80/20 mg	4:1
≥6 months, 10–<16 kg	120/30 mg	4:1
≥6 months, 16–<30 kg	200/50 mg	4:1
≥30 kg	400/100 mg	4:1

Upcoming new WHO dosing tables

No. of tablets or quantity of suspension by body weight band

3–5.9 kg (< 3 months)	3–5.9 kg (≥ 3 months)	6–9.9 kg (< 6 months)	6–9.9 kg (≥ 6 months)	10–14.9 kg	15–19.9 kg	20–24.9 kg	25–29.9 kg	30–34.9 kg	35–39.9 kg	40–44.9 kg	45–49.9 kg	≥ 50 kg
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DR-TB = in progress

- Harmonized weight and age approach
- Possibly also daily BDQ and harmonized loading and reloading strategies
- Possibly also daily DLM

Simplifying medicine dosing for children by harmonising weight bands across therapeutic areas

[Hylke Waalewijn, PhD^a](#) · [Mounier Almett, MSc^a](#) · [Roeland E Wasmann, PhD^a](#) · [Tim R Cressey, PhD^b](#) · [Prof Philippa Easterbrook, MPH^c](#) · [Peter Ehizibue Olumese, MD^d](#) · et al. [Show more](#)

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Weight (kg)	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	
Harmonised	3.0–5.9			6.0–9.9			10.0–14.9			15.0–19.9			20.0–24.9			25.0–29.9			30.0–34.9			35.0–39.9			40.0–44.9																		
Pocket Book for Hospital Care in Children	3.0–5.9			6.0–9.9			10.0–14.9			15.0–19.9			20.0–29.9			>30.0																											
WHO antibiotic book	3.0–5.9			6.0–9.9			10.0–14.9			15.0–19.9			20.0–29.9			>30.0																											
HIV	3.0–5.9			6.0–9.9			10.0–13.9			14.0–19.9			20.0–24.9			25.0–34.5			>35.0																								
Drug-susceptible tuberculosis		4.0–7.9			8.0–11.9			12.0–15.9			16.0–24.9			>25.0																													
Levofloxacin*				5.0–9.9			10.0–15.9			16.0–23.9			24.0–33.9			>34.0																											
3HP							10.0–15.9			16.0–23.9			24.0–30.9			31.0–33.9			>34.0																								
RR/MDR tuberculosis	3.0–4.9	5.0–6.9	7.0–9.9	10.0–15.9			16.0–23.9			24.0–29.9			30.0–35.9			36.0–45.9																											
Malaria																																											
A+L			5.0–14.9						15.0–24.9						25.0–34.9						>35.0																						
AS+SP			5.0–24.9												25.0–49.9																												
Primaquine				5.0–9.9			10.0–24.9									25.0–49.9																											
AS+MQ			5.0–8.9	9.0–17.9						18.0–29.9						>30.0																											
AS+AQ		4.5–8.9		9.0–17.9						18.0–35.9												>36.0																					
D+P			5.0–7.9	8.0–10.9	11.0–16.9			17.0–24.9						25.0–35.9						36.0–59.9																							
Hepatitis C virus																																											
SOF–DCV													14.0–25.9						>26.0																								
SOF–VEL	<17.0									17.0–29.9															>30.0																		
G–P	<20.0												20.0–29.9						30.0–44.9																								
SOF–LED	<17.0									17.0–34.9															>35.0																		

WHO consolidated guidelines on tuberculosis

Module 5: Management
of tuberculosis in children
and adolescents



WHO operational handbook on tuberculosis

Module 5: Management
of tuberculosis in children
and adolescents



WHO guidelines in children and adolescents

**The value of pharmacometrics
Example of BDQ**

2021

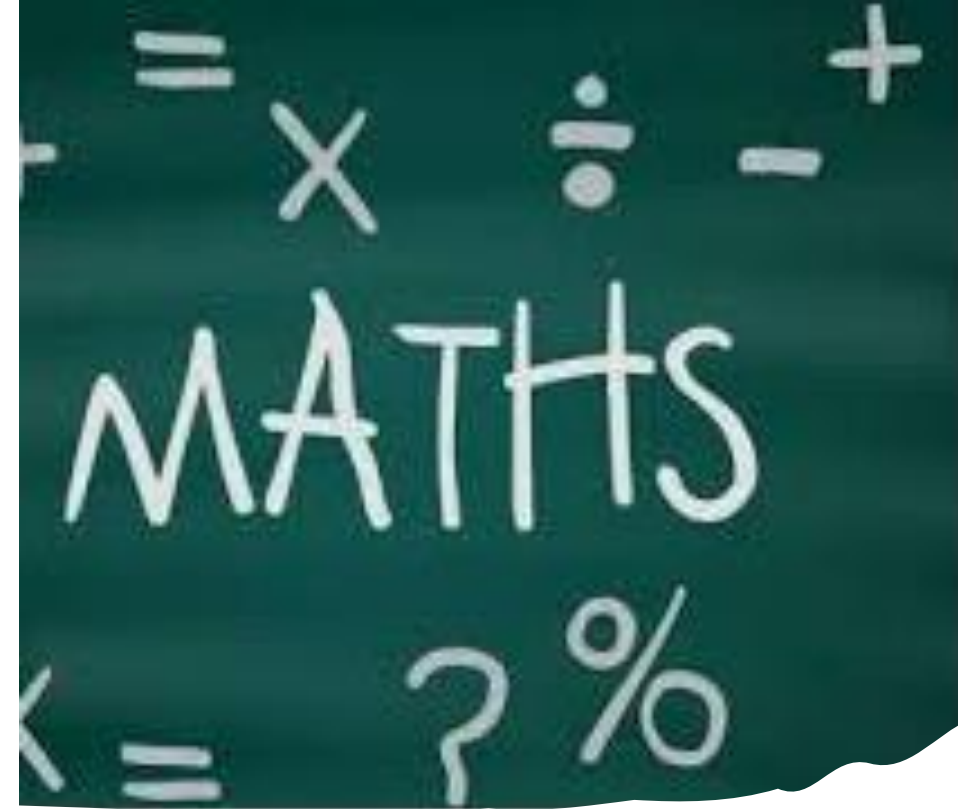
- **New drugs** for TB (Injectable sparing regimens)

But the reality:

- **No or limited PK data on**
 - bedaquiline in children < 6 years of age
- **Important safety considerations**



Groups & steps	Medicine	
Group A: Include all three medicines	Levofloxacin or Moxifloxacin	Lfx Mfx Bdq
	Bedaquiline	Bdq
	Linezolid	Lzd
	Clofazimine	Cfz
Group B: Add one or both medicines	cycloserine OR terizidone	Cs Tld
	ethambutol	E
	Delamanid	Dlm
	Pyrizinaide	Z
	imipenem-clastatin OR Meropenem	Ipem-Cln Mpm
	amikacin (OR streptomycin)	Am (S)
	ethionamide OR Prothionamide	Eto Pto
Group C: Add to complete the regimen and when medicines from Groups A and B cannot be used	p-aminosalicylic acid	PAS



Adult data

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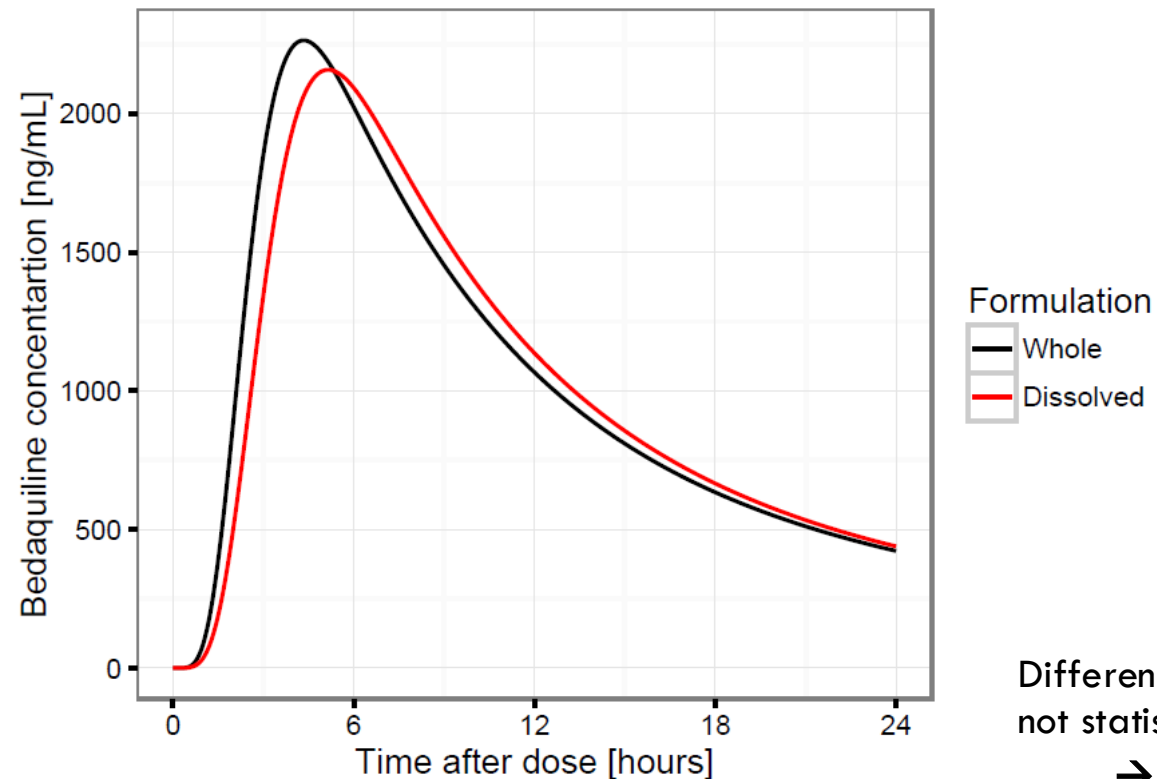
***limited* Paeds data (well-designed studies)**

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Pharmacometrics

PK modeling to bridge paediatric dosing –formulation access

BDQ CRUSH Impact of dissolving on a typical BDQ PK profile



- Mean absorption time slightly longer for dissolved tablets: +23% ($p=0.03$, $CI_{95\%}$ 2.1-48%)
- T_{max} : 4.3 to 5.2h
- C_{max} : ↓ 5%

Difference in bioavailability dissolved vs whole tablets not statistically significant ($p=0.92$, $CI_{95\%}$ 94-108%)

→ Bioequivalence criteria fulfilled



Svensson, BJ Pharm 2018



Methods (bedaquiline as example)



Elin Svensson

Bedaquiline PK key features

- Bioavailability increased two-fold with food
- Extremely long terminal half-life, >5 months
- **Metabolized by CYP3A4 to M2, same path for M2**
- Bedaquiline and M2 >99.9% and >99.7% protein bound
- PK-PD:
 - Average bedaquiline concentrations linked to rate of bacterial clearance
 - M2 linked to QT prolongation

Report of a WHO expert consultation on dosing to enable implementation of treatment recommendations in the WHO consolidated guidelines on the management of TB in children and adolescents. Geneva: World Health Organization; 2022. Licence: CC BY-NC-SA 3.0 IGO.

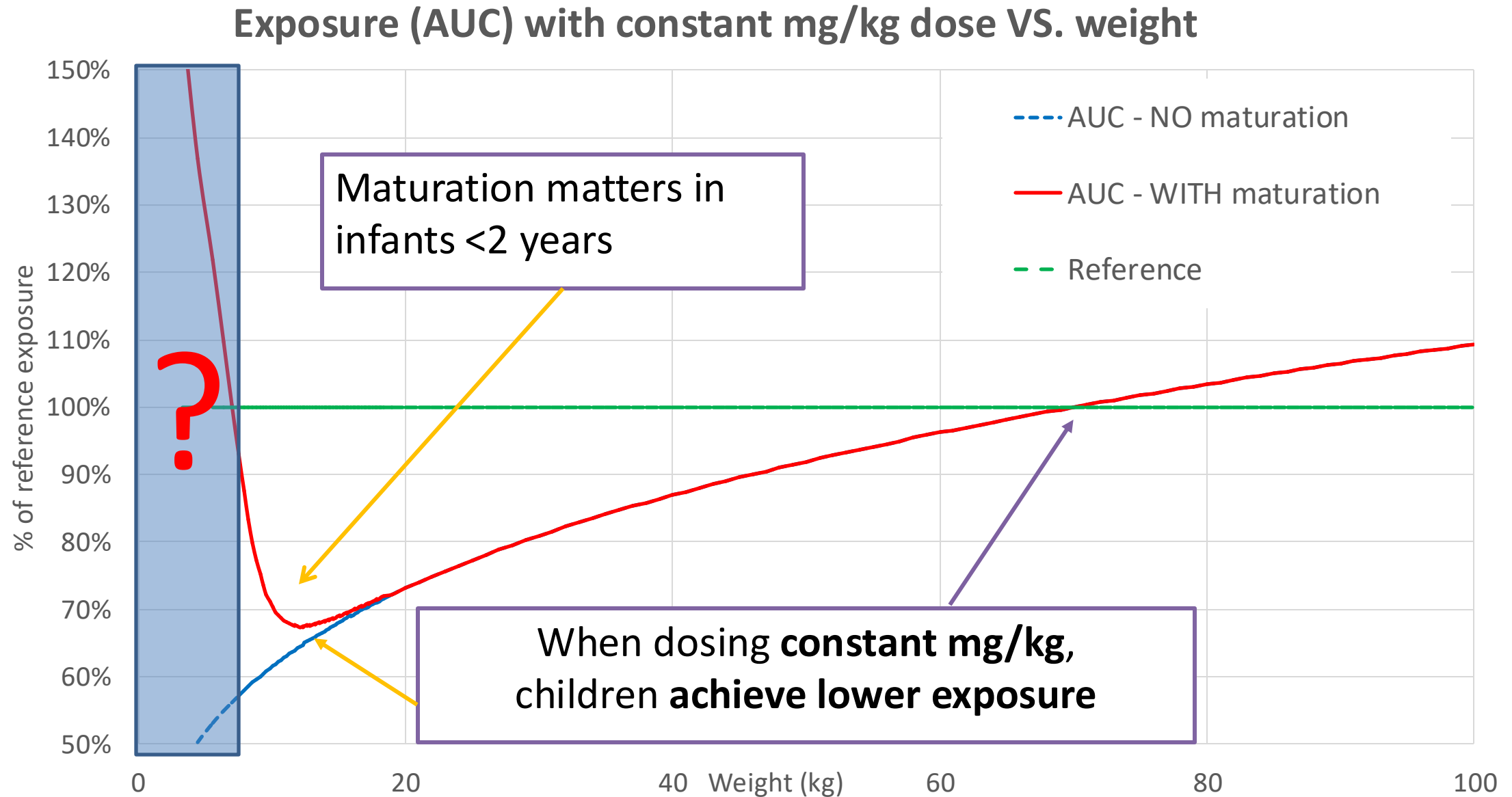
Heeswijk et al. J Antimicrob Chemother. 2014;69(9):2310-8.

Tanneau et al. CPT Pharmacometrics Syst Pharmacol. 2021.

Liu et al. Drug Metab Dispos. 2014;42(5):863-6.

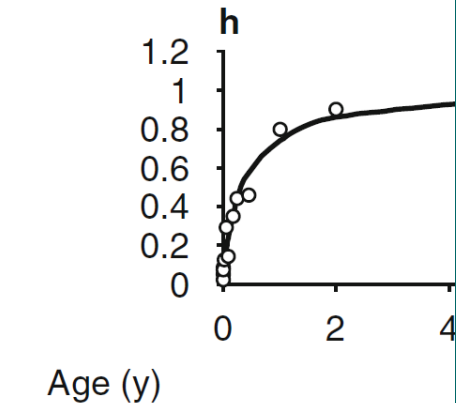
Svensson et al. J Antimicrob Chemother. 2017;72(12):3398-405.

Allometry predicts **higher** maintenance dose/kg in children



Johnson et al. based on measurements of enzyme expression and activity in post-mortem livers

Salem et al. based on a clearance, a compound



Prediction of the Clearance of Eleven Drugs and Associated Neonates, Infants and

Trevor N. Johnson, Amin Rostami-Hodjegan

A Review for CYP3A4

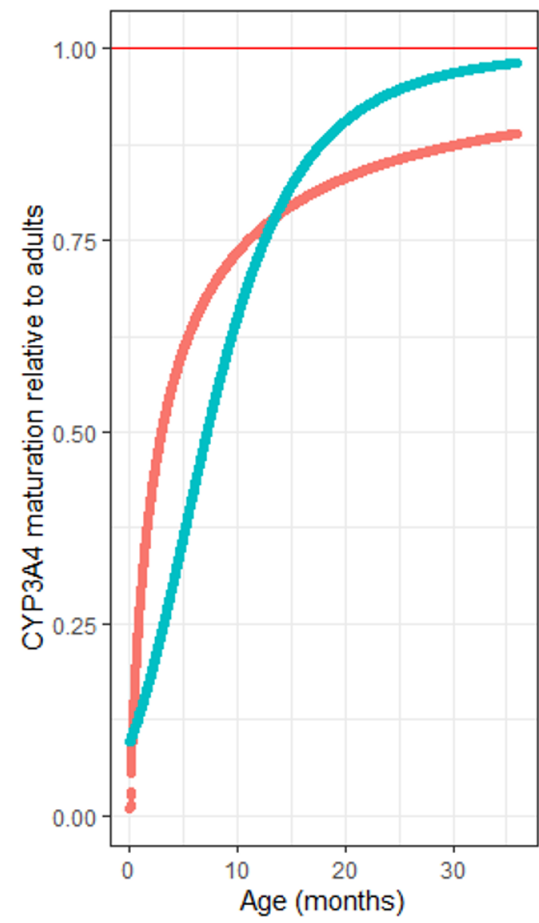
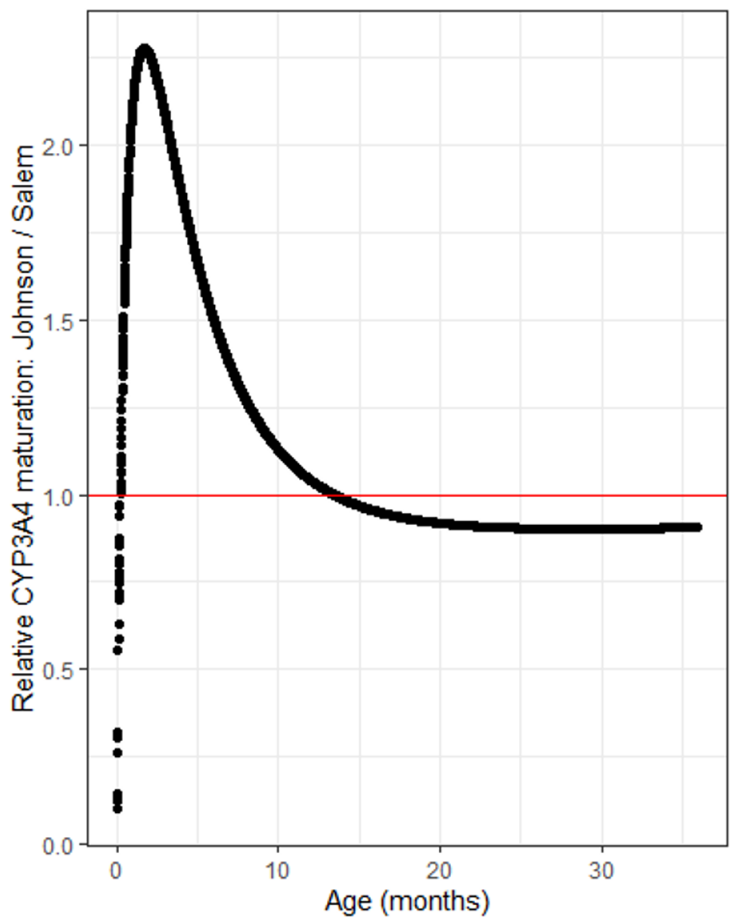
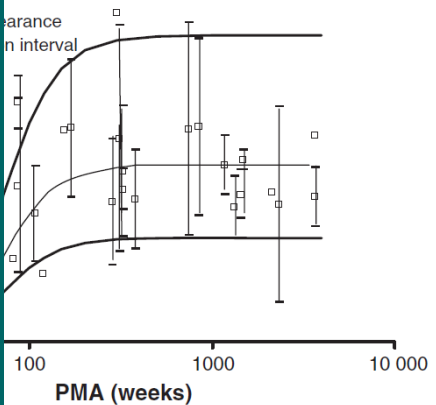


Figure 11. Maturation functions CYP3A4.



uration clearance (CL) parameter estimates. er variability is shown as CV%, SE is the structural parameter, and 95%CI is the 95% e structural parameter estimate

Estimate	CV	SE	95%CI
523	32%	4.5%	469, 579
73.6	—	7.5%	59.4, 80.0
3	—	19.4%	2.2, 4.1
0.0005	—	51.6%	0.0009, 0.003

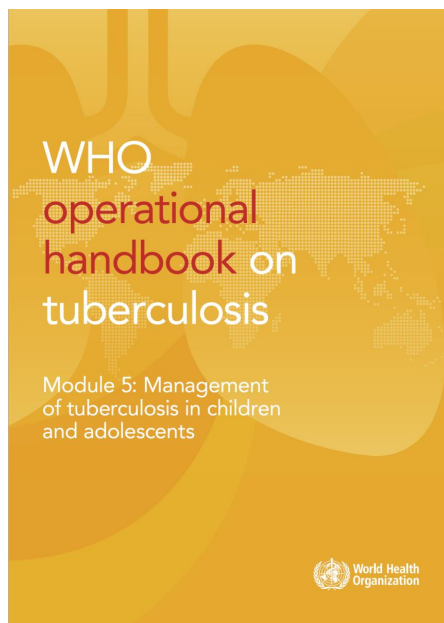


uration changes with age. Estimates from with standard deviation, when reported.

A maturation model for midazolam clearance Brian J. Anderson¹ & Peter Larsson²

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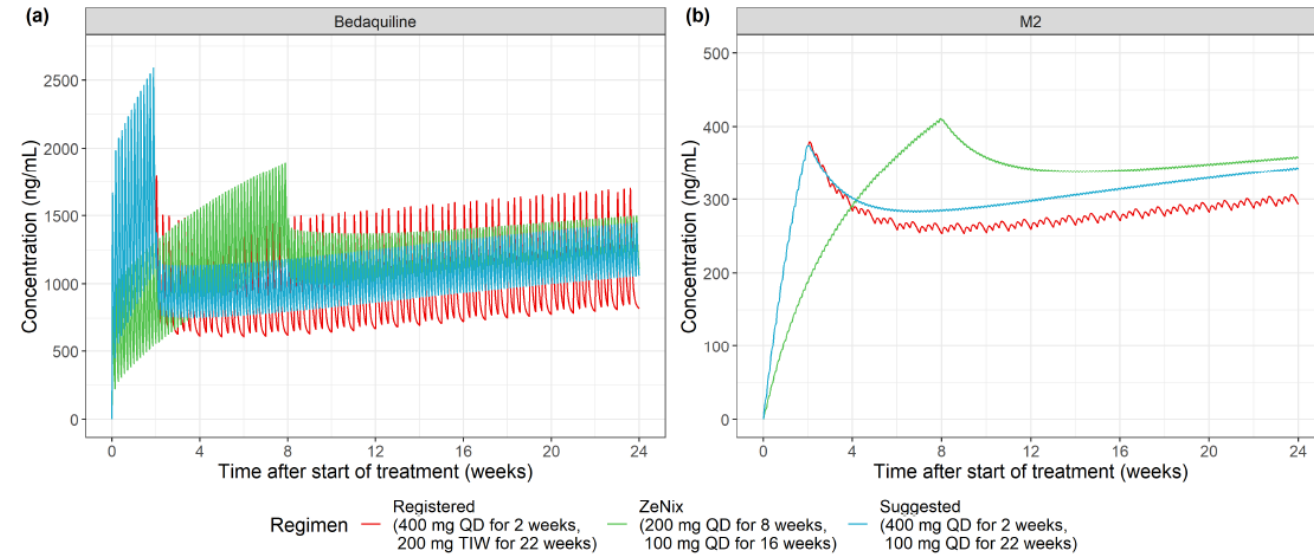
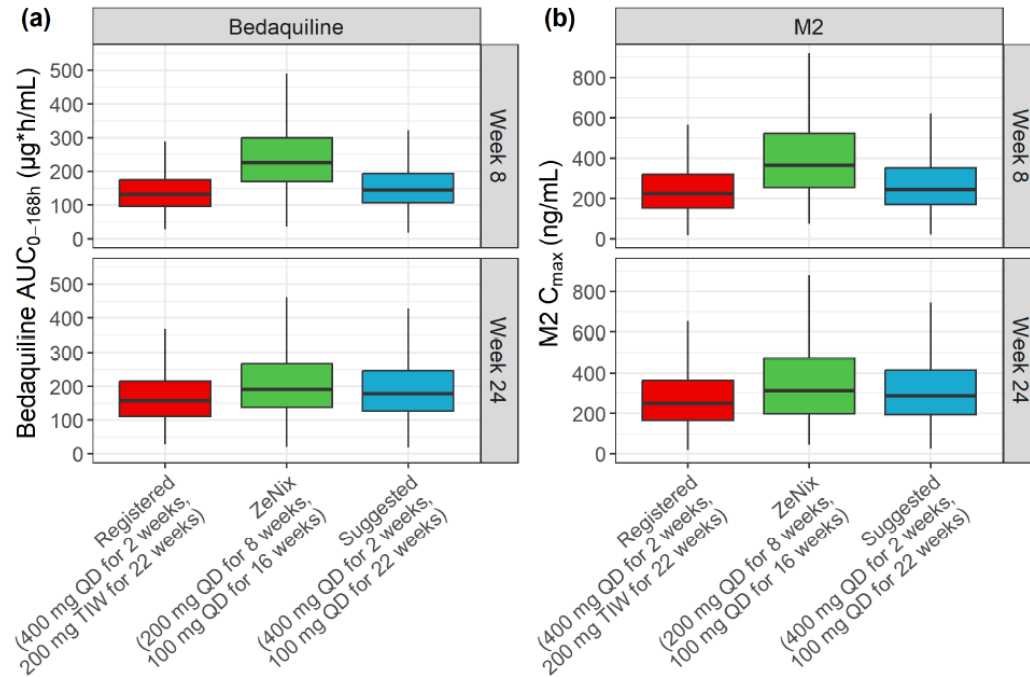
Group	Medicine	Weight-based daily dose ^b	Formulations (mg/mL, as applicable)	Weight bands ^a								Usual upper daily dose ^b	Comments
				3 to <5 kg	5 to <7 kg	7 to <10 kg	10 to <16 kg	16 to <24 kg	24 to <30 kg	30 to <36 kg	36 to <46 kg		
A	Levofloxacin	15–20 mg/kg	100 mg dt	5 mL (0.5 dt)	1	1.5	2	3	-	-	-	1.5 g	
			250 mg tab (250 mg in 10 mL = 25 mg/mL)	2 mL ^c	5 mL (0.5 tab) ^c	5 mL (0.5 tab) ^c	1	1.5	2	3	3	1.5 g	
	Moxifloxacin	10–15 mg/kg (standard dose) ^d	100 mg dt (100 mg in 10 mL = 10 mg/mL)	4 mL	8 mL	1.5	2	3	4	4	4	400 mg	
			400 mg tab (400 mg in 10 mL = 40 mg/mL)	1 mL ^c	2 mL ^c	3 mL ^c	5 mL ^c (0.5 tab)	7.5 mL ^c (0.75 tab)	1	1	1	400 mg	
		High dose ^d	400 mg tab	-	-	-	-	-	-	1 or 1.5	1.5	800 mg	
	Bedaquiline	-	20 mg dt ^e	0 to <3 months: 1.5 od for 2 weeks; then 0.5 od M/W/F for 22 weeks ≥ 3 months: 3 od for 2 weeks; then 1 od M/W/F for 22 weeks	0 to <3 months: 1.5 od for 2 weeks; then 0.5 od M/W/F for 22 weeks 3 to <6 months: 3 od for 2 weeks; then 1 od M/W/F for 22 weeks ≥ 6 months: 4 od for 2 weeks; then 2 od M/W/F for 22 weeks	3 to <6 months: 3 od for 2 weeks; then 1 od M/W/F for 22 weeks ≥ 6 months: 6 od for 2 weeks; then 3 od M/W/F for 22 weeks	10 od for 2 weeks; then 5 od M/W/F for 22 weeks	20 od for 2 weeks; then 10 od M/W/F for 22 weeks	-	-	-	-	A daily loading dose is used for the first 2 weeks, followed by a maintenance dose given three times a week
		-	100 mg tab ^e	0 to <3 months: 3 mL od for 2 weeks; then 1 mL od M/W/F for 22 weeks ^c ≥ 3 months: 6 mL od for 2 weeks; then 2 mL od M/W/F for 22 weeks ^c	0 to <3 months: 3 mL od for 2 weeks; then 1 mL od M/W/F for 22 weeks ^c 3 to <6 months: 6 mL od for 2 weeks; then 2 mL od M/W/F for 22 weeks ^c ≥ 6 months: 8 mL od for 2 weeks; then 4 mL od M/W/F for 22 weeks ^c	3 to <6 months: 6 mL od for 2 weeks; then 2 mL od M/W/F for 22 weeks ^c ≥ 6 months: 12 mL od for 2 weeks; then 6 mL od M/W/F for 22 weeks ^c	2 od for 2 weeks; then 1 od M/W/F for 22 weeks	4 od for 2 weeks; then 2 od M/W/F for 22 weeks	-	-	-	-	

Adults

Daily dosing (adults)

Model-Informed Once-Daily Dosing Strategy for Bedaquiline and Delamanid in Children, Adolescents and Adults with Tuberculosis

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Full concentration-time profiles of (a) bedaquiline, (b) M2, (c) delamanid and (d) DM-6705 over time for a reference individual (32-year-old, non-black race, 56.6 kg and 3.65 g/dL of albumin level at baseline). BID, twice daily; QD, once daily; TIW, thrice weekly.

BDQ reloading (adults)

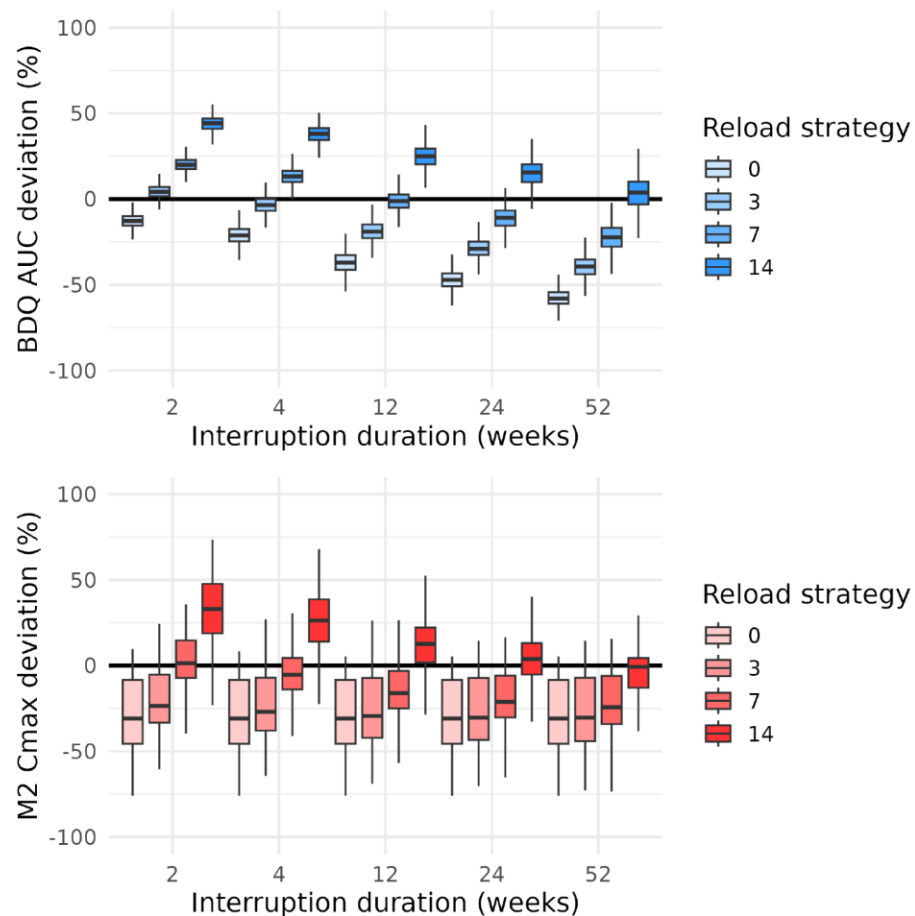


FIG 2 Boxplots of the BDQ AUC deviation after reloading (upper) and M2 C_{max} deviation after treatment restart (lower), stratified by interruption duration and colored by reloading strategy, for interruptions starting after 8 weeks of daily dosing BDQ treatment with an initial 2-week 400 mg once-daily loading phase. The boxplots depict the median and interquartile range, with the whiskers extending to the most extreme values within 1.5x interquartile range.

TABLE 1 Optimized bedaquiline reloading strategies following interruptions of once-daily 100 mg bedaquiline regimens

Interruption duration	Optimized reloading strategy
Daily dosing regimen starting with 2 weeks of loading	
<1 week	No reloading
1–4 weeks	3 days 400 mg bedaquiline daily
4–26 weeks	7 days 400 mg bedaquiline daily
≥26 weeks	14 days 400 mg bedaquiline daily



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Bedaquiline reloading strategies following interruptions during daily dosing

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