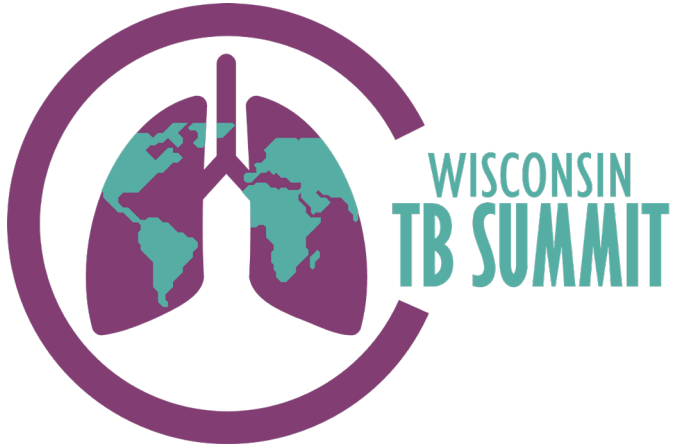

THERAPEUTIC DRUG MONITORING IN TB

KEY CONCEPTS AND PRACTICAL APPLICATIONS

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DISCLOSURES

- No relevant financial disclosures
- Off-label mention:
  - Clofazimine for TB
  - Levofloxacin for TB
  - Moxifloxacin for TB
  - Rifabutin for TB
  - Amikacin for TB

LEARNING OBJECTIVES

- Review key concepts of therapeutic drug monitoring (TDM)
- Identify TB cases that require TDM
- Interpret TDM results and adjust drug therapy appropriately

THERAPEUTIC DRUG MONITORING (TDM)

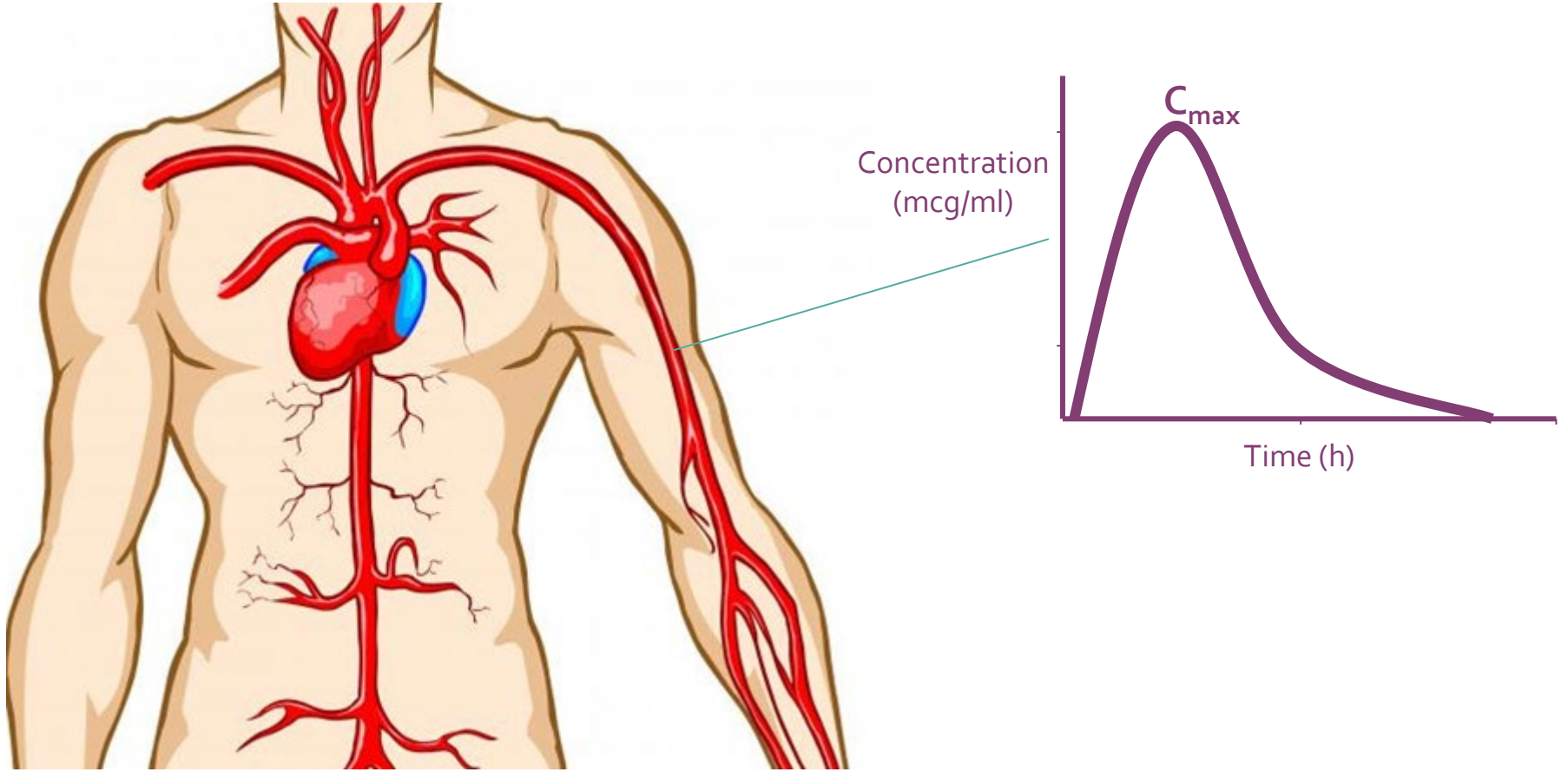
1

WHAT, WHY, AND WHO

WHAT IS THERAPEUTIC DRUG MONITORING?

- Measuring drugs levels
- Designated intervals
- Target concentrations/range
- Optimize dosage regimen

BLOOD LEVELS = SURROGATE MARKER



WHY DO DRUG LEVELS IN TB?

- Efficacy target
- Minimize toxicity
- Compliance measure
- Confirm absorption
- Assess degree/presence of drug interaction

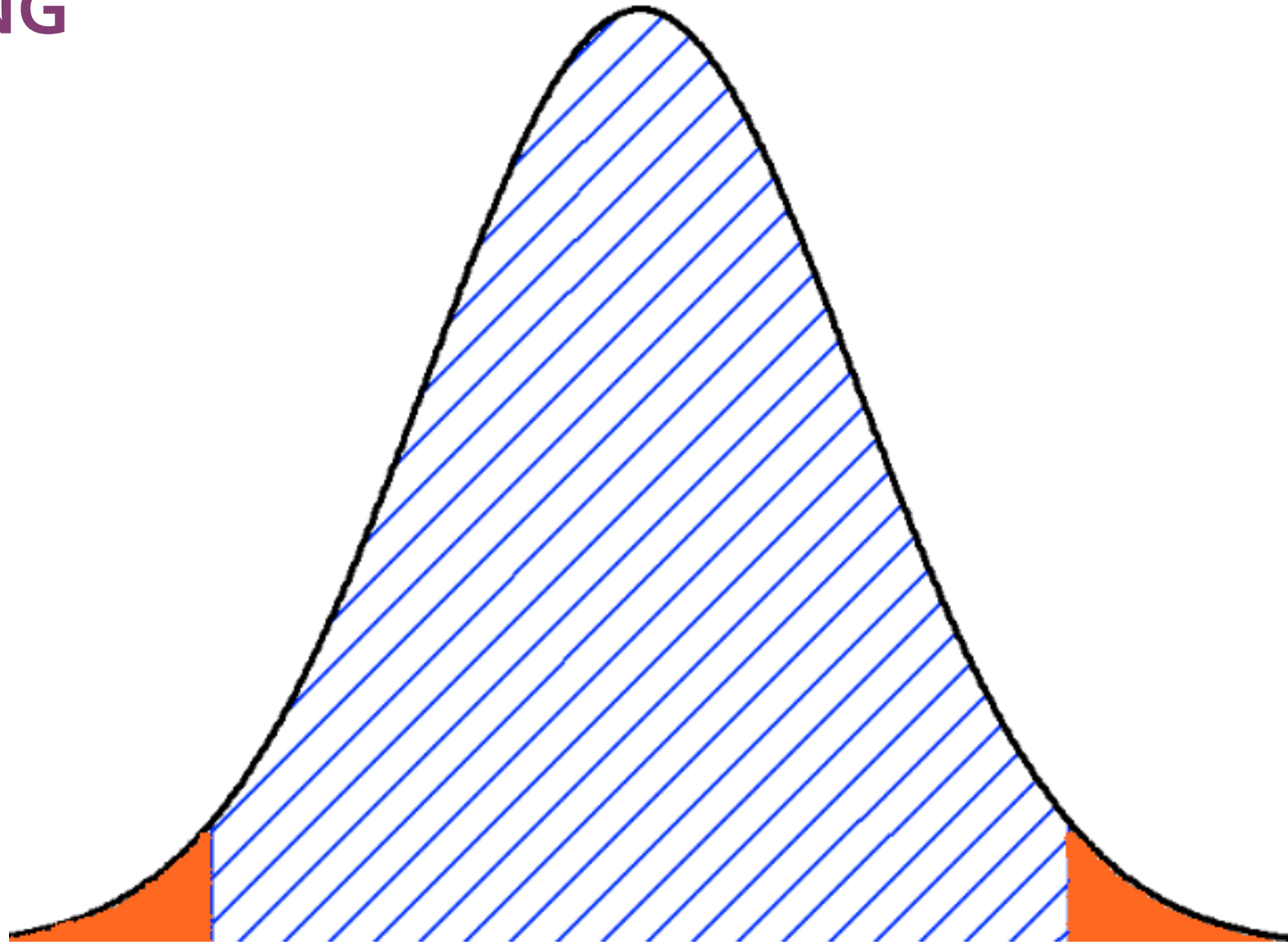
ANTIMICROBIAL DOSE DETERMINATION

- Pre-clinical
  - Microbiology
  - PK/PD targets
  - Animal models
- Phase 1
  - Human pharmacokinetics
  - Safety
  - Maximum tolerated dose
- Monte Carlo simulations
- PTA, MIC distribution, CFR
- Phase 2 + 3
- Dosing schema
- Efficacy/safety
- Clinical validation

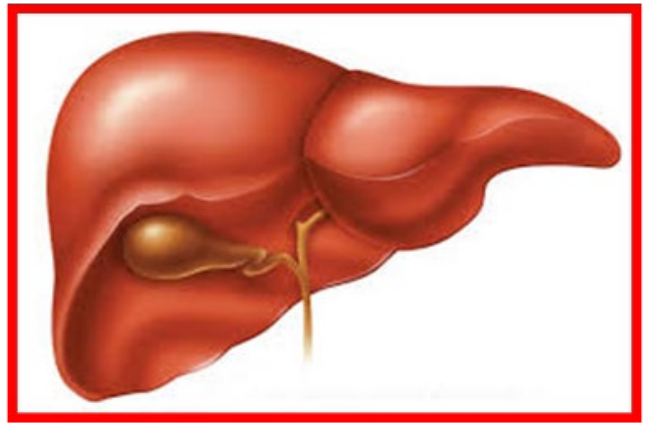
STANDARD DOSING

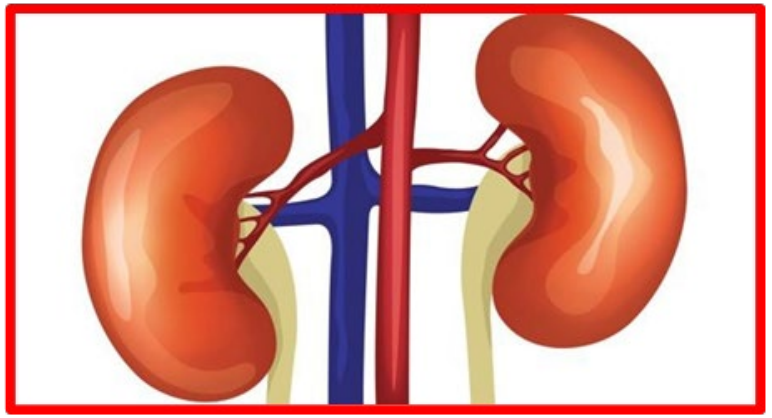
Mean

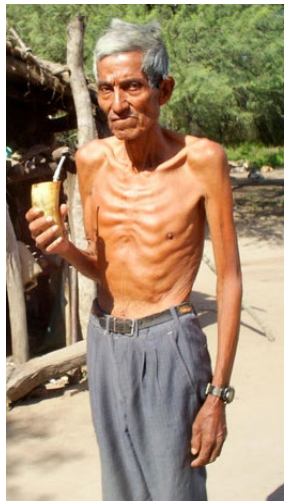
Majority

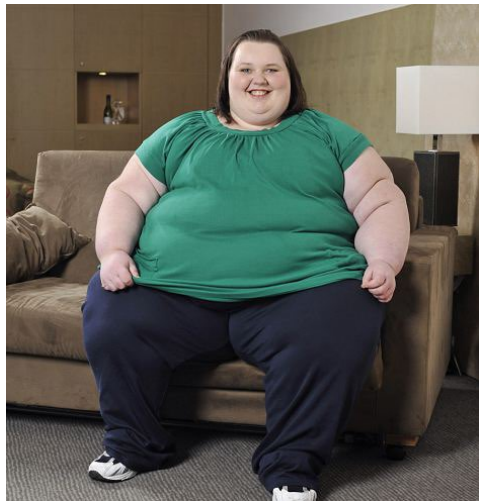


SAME DOSE FOR ALL?







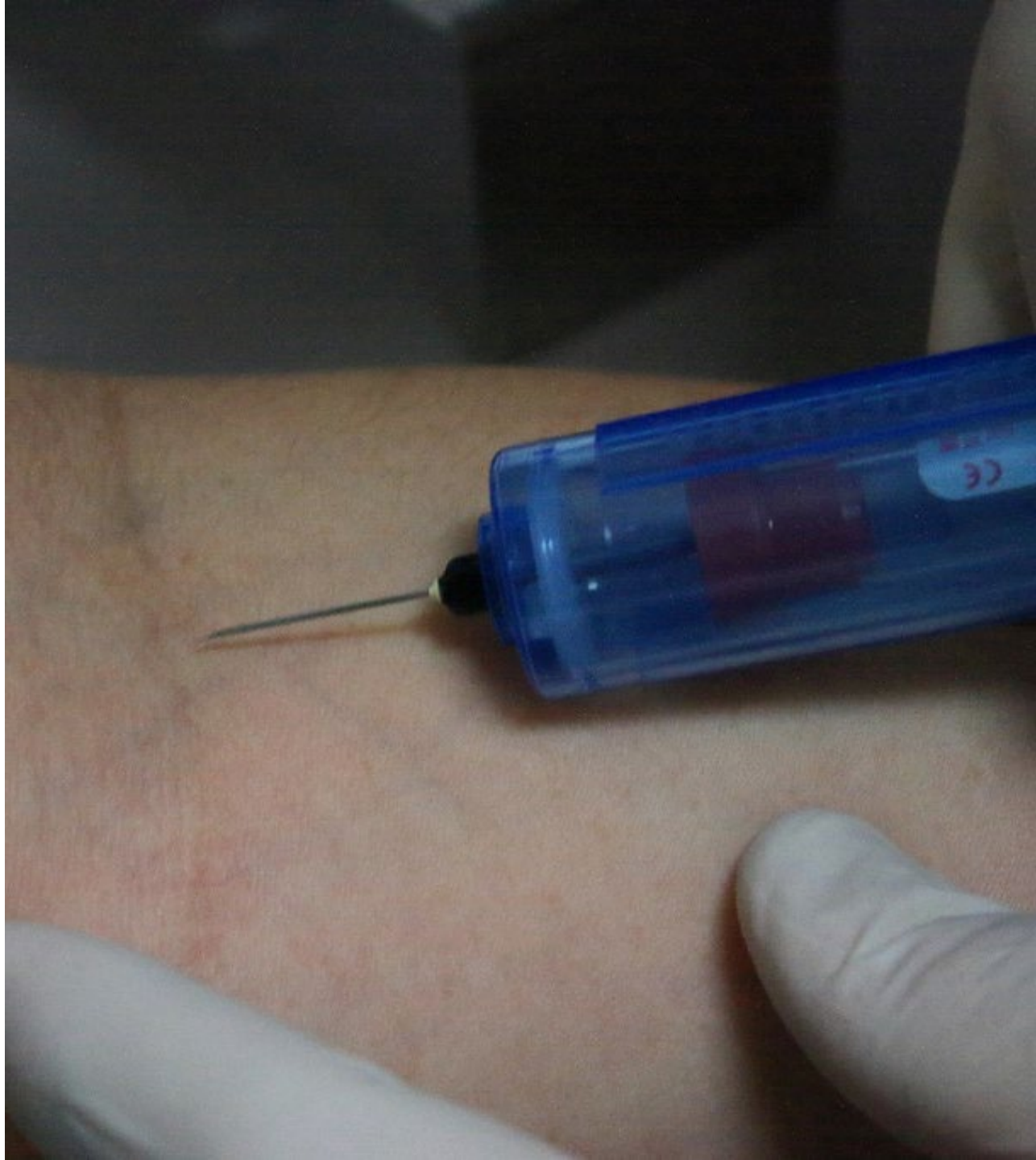


FIND THE OUTLIERS

- **Standard TB drug doses**
  - Anticipated exposure
  - Expected outcome

- **TDM**
  - Target serum exposure
  - Individualize treatment

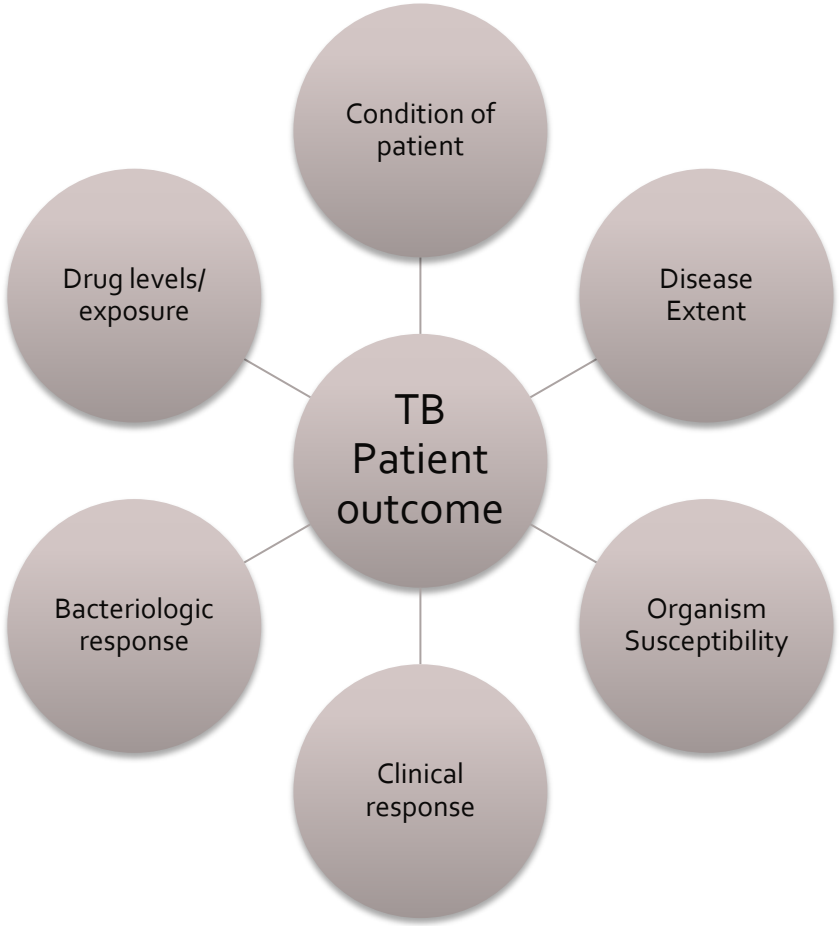
TDM = More information



TDM - NOT A MAGIC BULLET

✓	Normal Exposure	Toxicity Clinical Failure
$	Cost	
👁	Resource intensive	
🧪	Laboratory/Assay Availability	
⚠	Data deficiencies	

CONTRIBUTION TO PATIENT OUTCOME



DATA PROGRESS OF TDM POTENTIAL IN TB

- **TB slow clinical response ? TDM eval**
  - Majority = low 2h level of TB therapy[1]
    - RIF (52%), INH (59%), and EMB (31%)
  - 17 of 20 (85%) had a low drug concentrations[2]
    - All = delayed culture conversion
- **TDM Cohort - outcome comparison**[3]
  - ↑ Therapy failure with low:
    - RIF (p=0.04), INH (p=0.04), RIF + INH (p =0.005)
- **Low drug level + increased dose ? culture conversion/clinical response**[4]

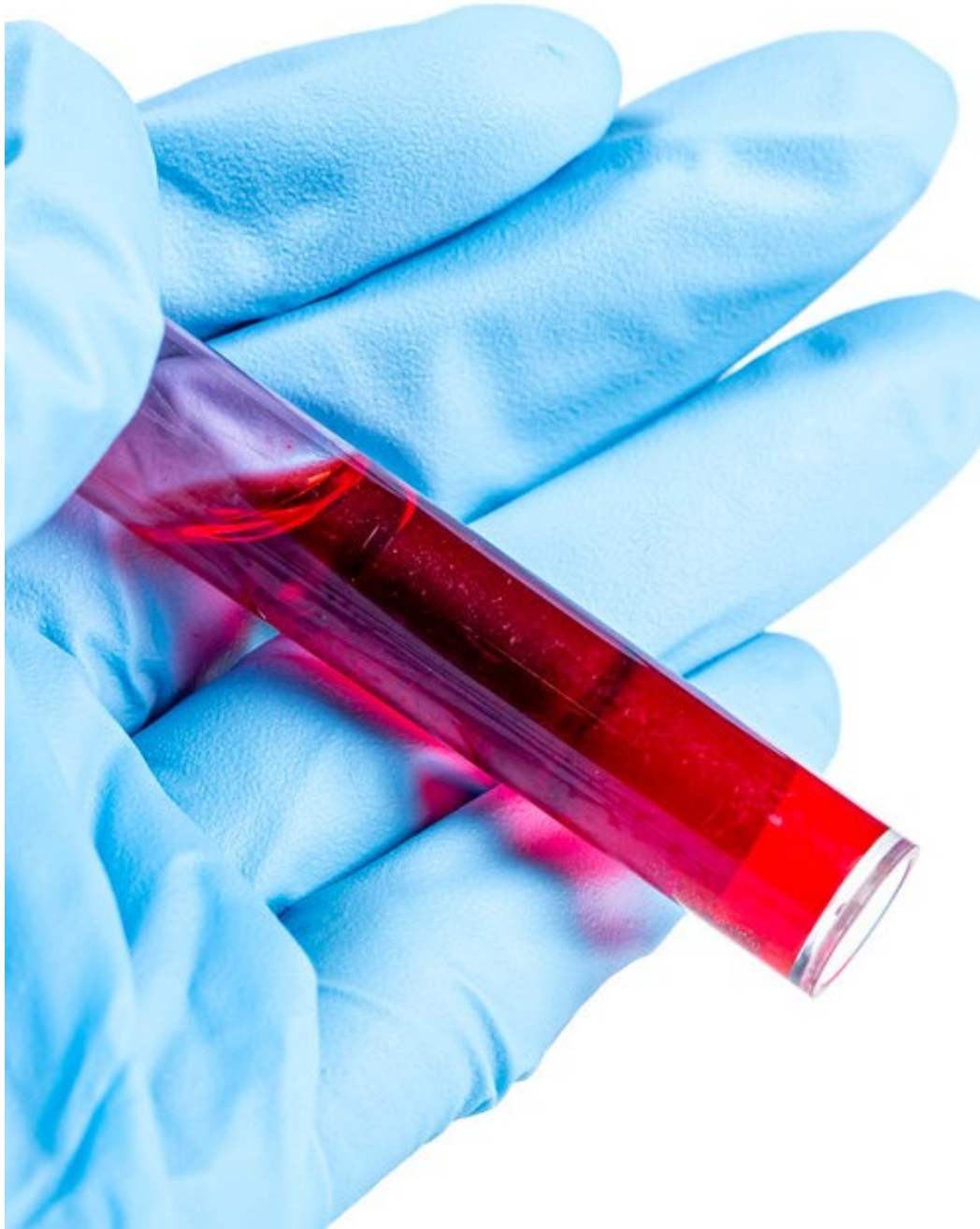
1. Heysell et al. Emerg Infect Dis. 2010; 16(10):1546–53
2. Babalik et al. Can Respir J. 2011;18(4):225–9. (31)
3. Prahl et al. J Antimicrob Chemother. 2014; 69(10):2841-7
4. Magis-Escurra et al. Pulm Pharmacol Ther. 2012;25(1):83–6

TDM FOR WHOM?

- Slow responders (> 2-3wk - smear positive)
- Extremes of weight (low/high)
- Impaired renal/hepatic/drug clearance
- Concerning drug interactions
- Malabsorption potential
- Elevated drug toxicity risk

“ALL MODELS ARE APPROXIMATIONS. BUT SOME ARE USEFUL.”

-GEORGE BOX



SUMMARY

- **Blood level assessment:**
  - Informs drug exposure
- **Standard TB drug doses**
  - Anticipated exposure
  - Expected outcome
- **Outliers exist**
- **TDM**
  - Individualized drug exposure information
  - May enhance TB outcome
- **TDM candidates**
  - Slow TB response
  - High/low exposure potential
  - Drug resistance

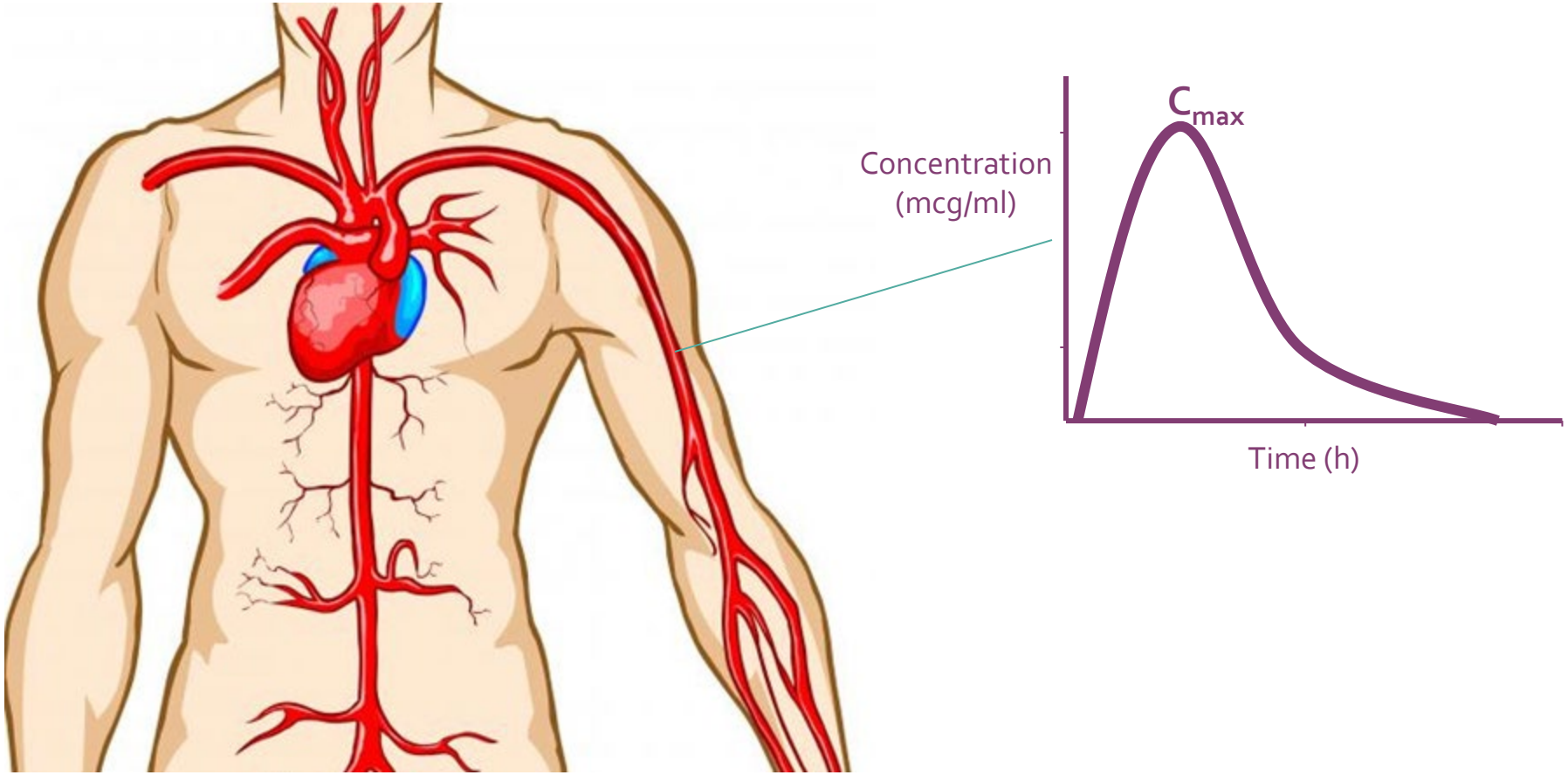
WHICH PATIENT SCENARIO WOULD LEAST LIKELY SEE BENEFIT FROM SERUM DRUG LEVEL ASSESSMENT OF ORAL TB THERAPY?

A	Rifabutin (CYP3A4 substrate) + Darunavir/Ritonavir (CYP3A4 inhibitors)
B	Chronic liver disease (Child's Pugh C), ascites, and low body weight (45kg)
C	Non-cavitary, drug-sensitive TB. 70kg. Otherwise, healthy
D	MDR TB with history of small bowel resection

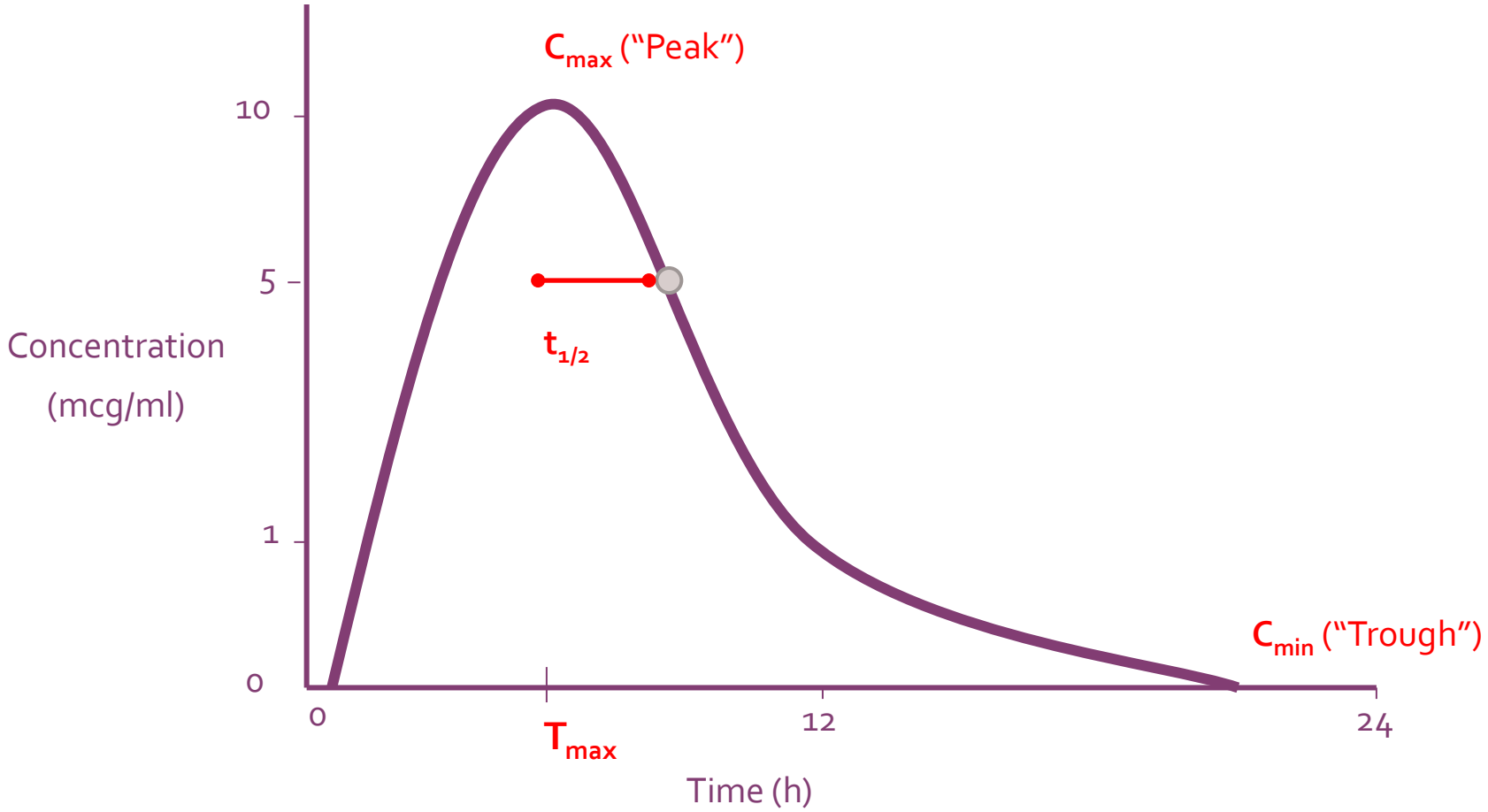
HOW TO PERFORM TDM?

2

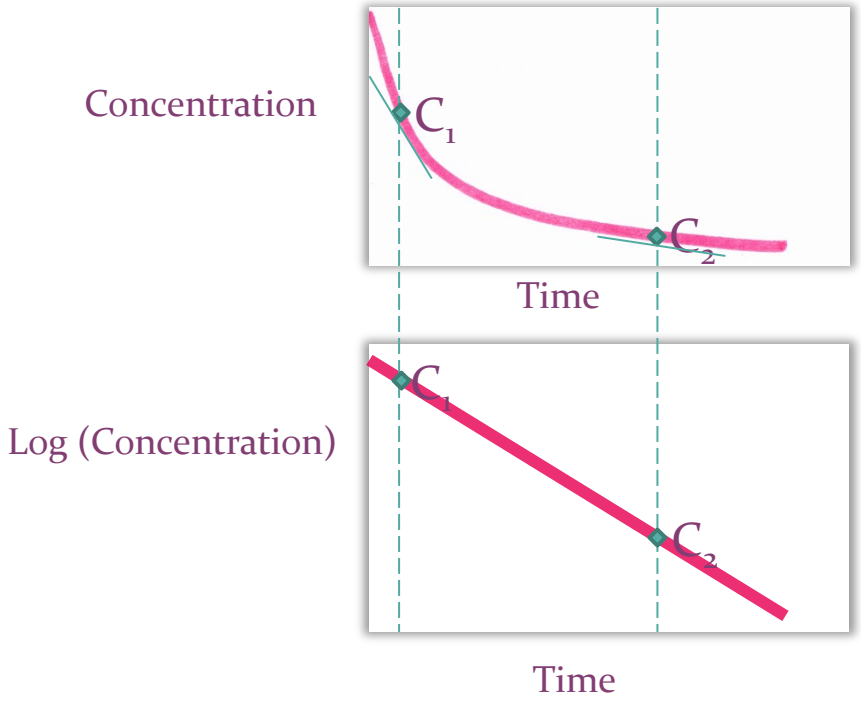
BLOOD LEVELS = SURROGATE MARKER

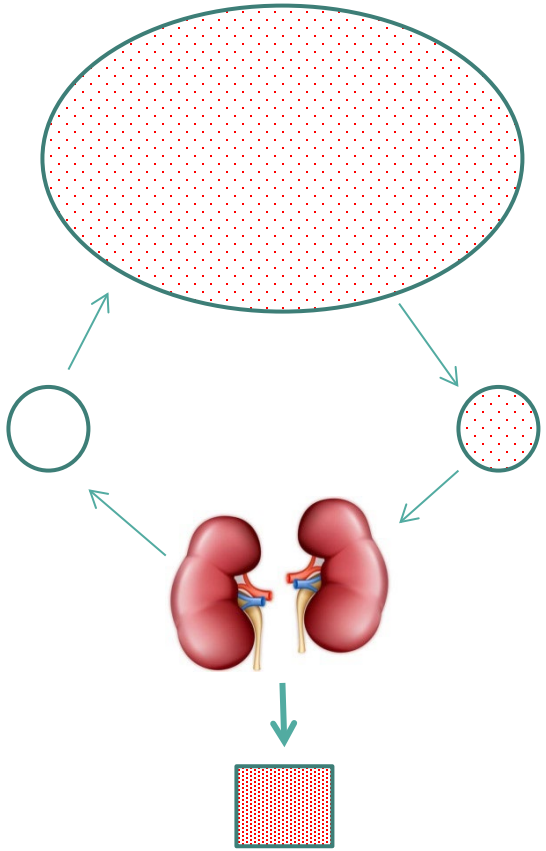


PHARMACOKINETIC TERMS

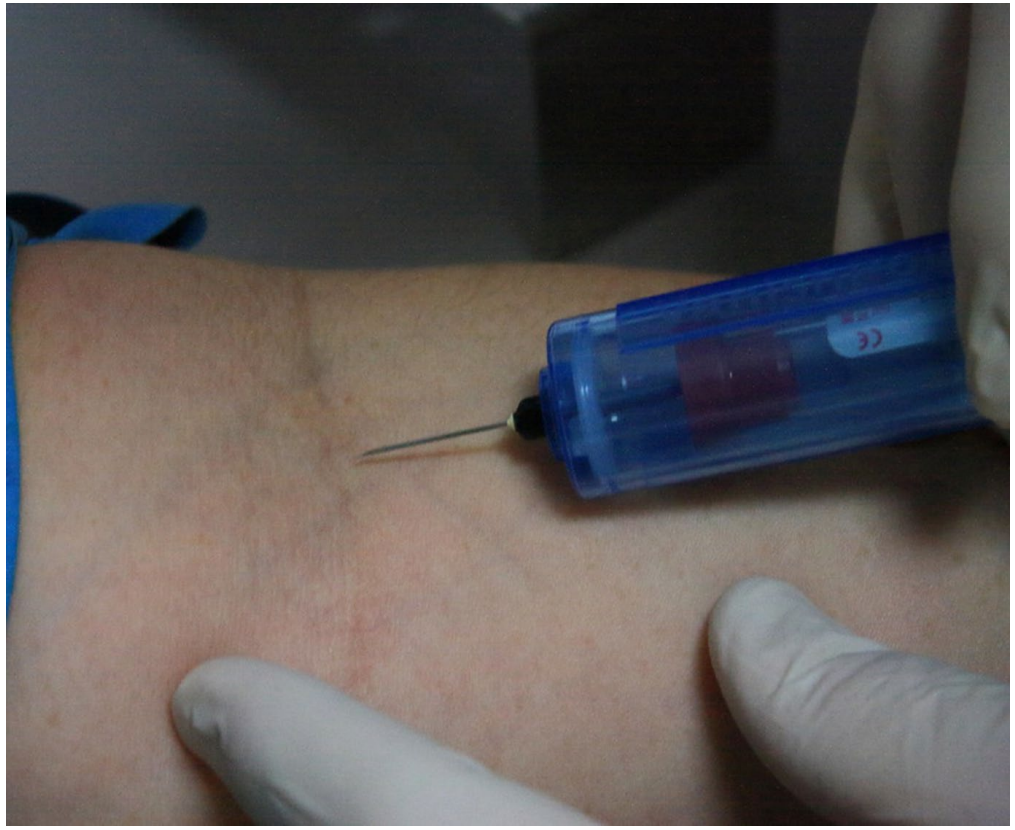


FIRST ORDER KINETICS





WHEN TO DRAW BLOOD FOR ORAL TB TDM

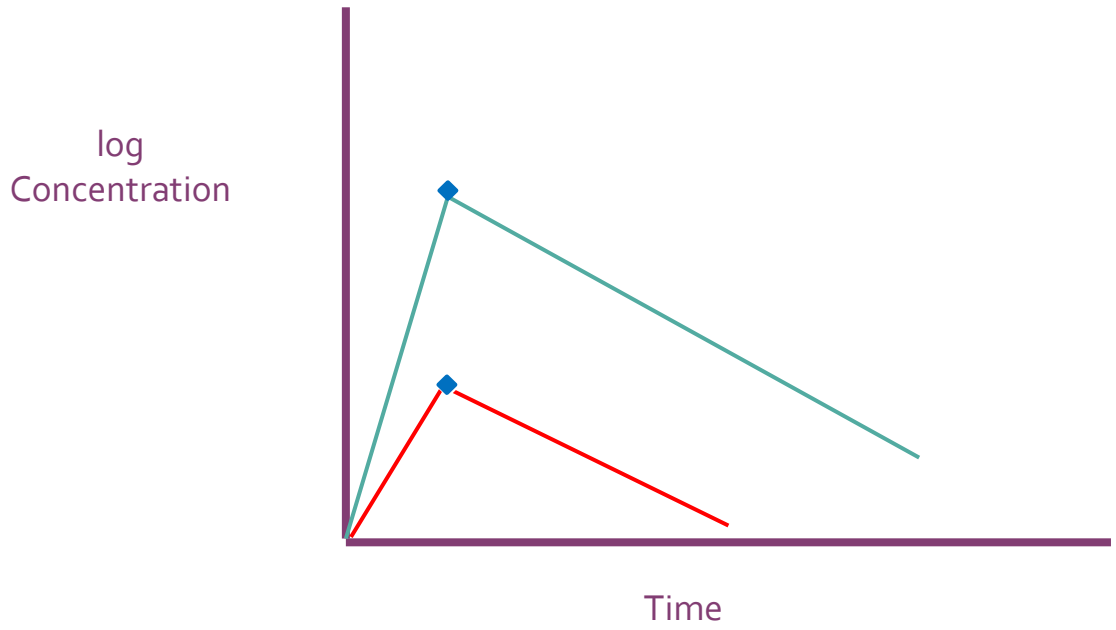


PEAK (C_{MAX}) BLOOD DRAWS

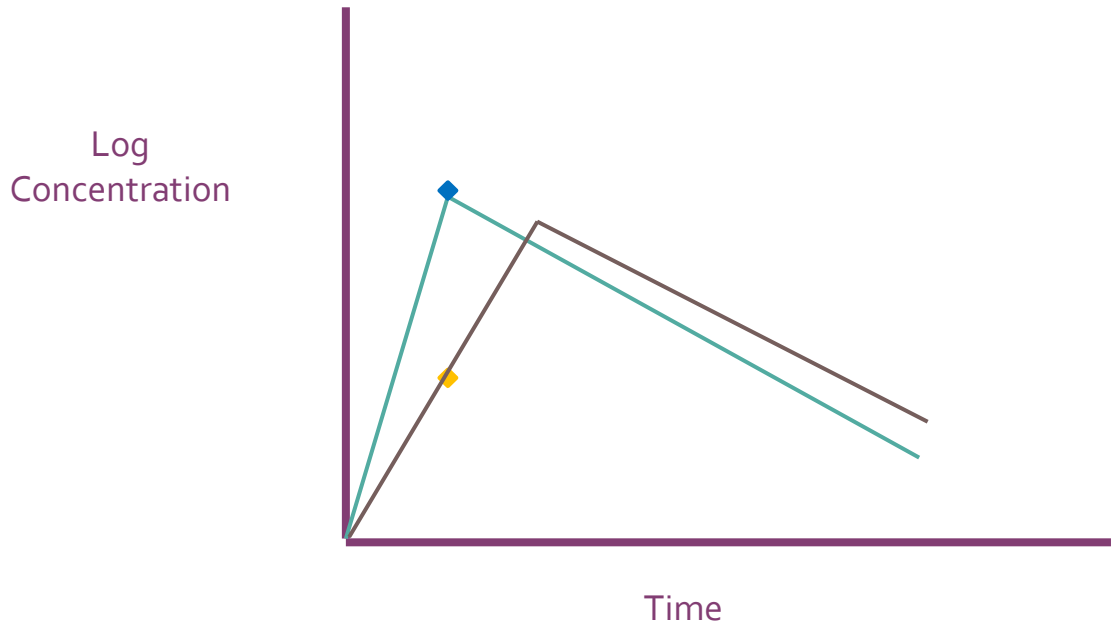
- **TWO(2)-hour post oral dose blood sample**
  - Approximates "peak" in most oral TB drugs
    - T_{max} close to 2 hours
  - Absorption information

- Trough levels
  - Many TB drugs often below assay detection limit

SINGLE ASSESSMENT- MALABSORPTION



SINGLE ASSESSMENT – DELAYED ABSORPTION



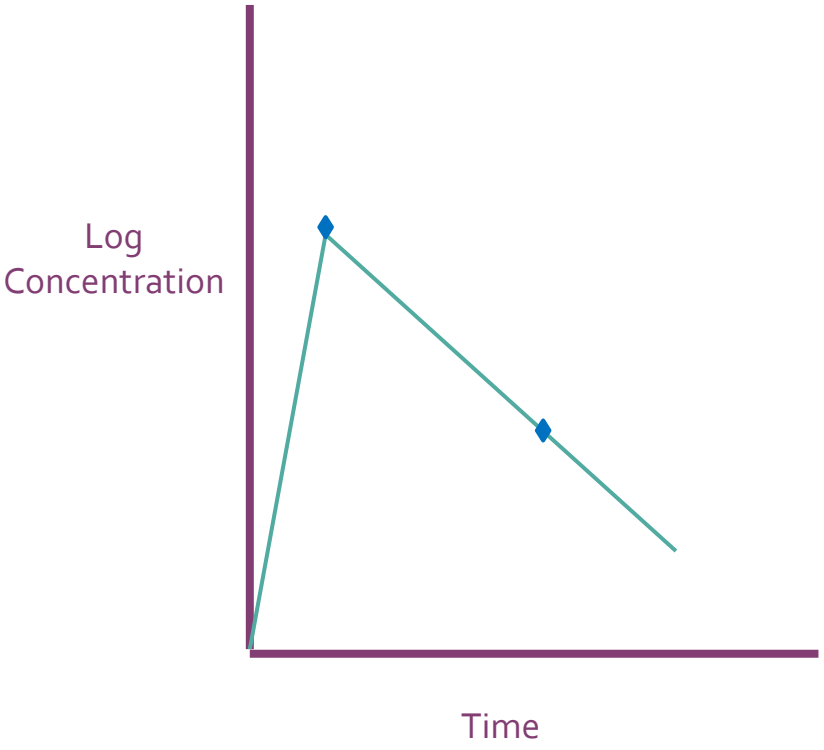
TWO ASSESSMENTS = IMPROVED INFORMATION

- **Adding a 6-hour post oral dose blood sample**
  - Rate + extent of absorption
  - Elimination/drug clearance
  - Malabsorption vs delayed absorption

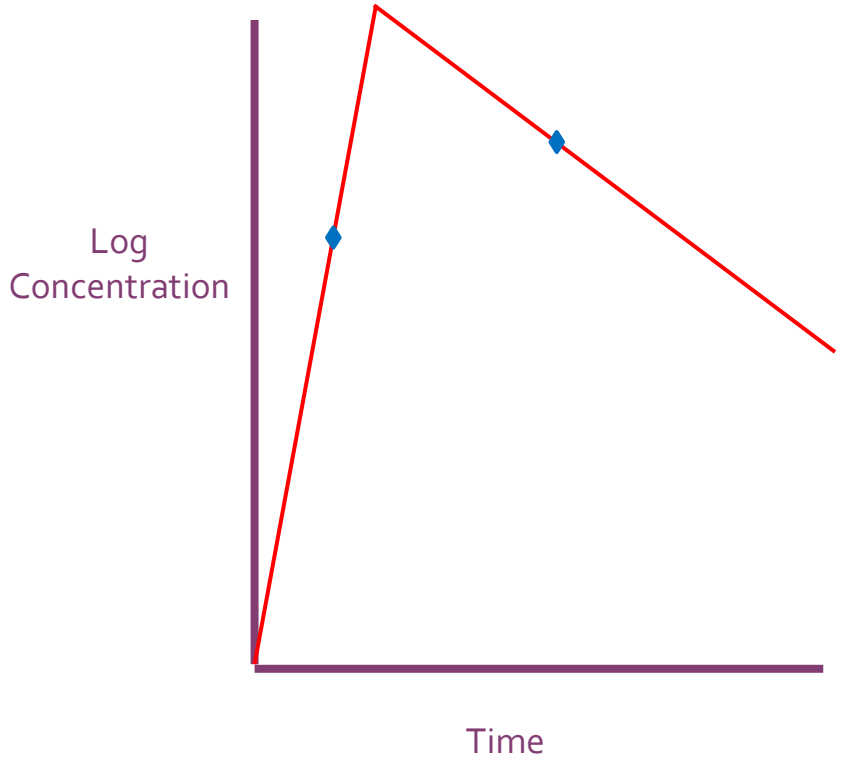
- **Two assessments: 2-hour + 6-hour post oral dose blood samples**
  - Preferred approach for most oral TB therapies

2-HOUR + 6-HOUR POST ORAL DOSE LEVELS

Drug Clearance information

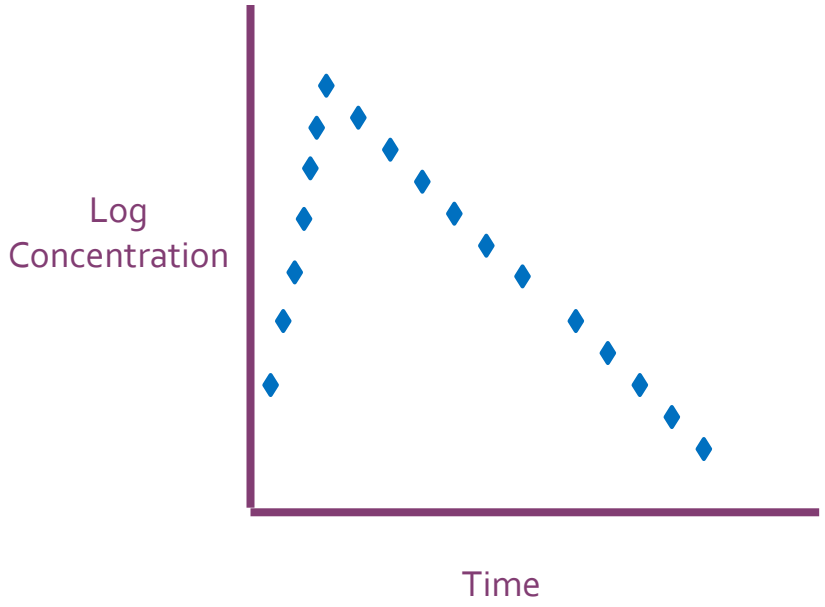


Slow/Delayed absorption



DUAL ASSESSMENT: 2H AND 6H LIMITATIONS

- Still only 2 time points



BLOOD ASSESSMENTS: DRUG NUANCES

Drug	Peak Assessment (hours)	Additional Assessment (hours)
Bedaquiline	5	24*
Clofazimine	2-3	6-7
Cycloserine	2-3	6-7
Ethambutol	2-3	6-7
Ethionamide	2	6
Isoniazid	1-2	4-6
Levofloxacin	2	6
Linezolid	2	5-6, 24*

Drug	Peak Assessment (hours)	Additional Assessment (hours)
Moxifloxacin	2	6
Para-amino salicylic acid	6	-
Pretomanid	5	24*
Pyrazinamide	2	6
Rifabutin	3-4	7
Rifampin	2	6
Rifapentine	5-6	24*

* Trough level can be taken immediately before dose

Tables adapted from: Drug-Resistant Tuberculosis: A Survival Guide for Clinicians, Third Edition/ 2022 Updates. Curry TB Center

SUMMARY-TDM APPROACH MOST ORAL TB DRUGS

- Dual blood level assessment
  - 2-hour and 6-hour post oral doses
- Consider PK of specific drugs during interpretation
- Add trough
  - Bedaquiline
  - Linezolid
  - Pretomanid
  - Rifapentine

RIFAMPIN, ISONIAZID, PYRAZINAMIDE AND ETHAMBUTOL ADMINISTERED AT 0800

WHEN SHOULD BLOOD LEVELS BE DRAWN?

A	0730 and 1200
B	0800 and 1000
C	1000 and 1400
D	0900 and 1100

ORAL TDM CASES 3

CASE – INH/EMB RESISTANCE

- 31 yo F (74kg) with bilateral non-cavitary pulmonary TB
  - INH and EMB resistance
  - Normal kidney/liver function.
  - No comorbidities.
    - Regimen updated to:
      - **Rifampin 600mg daily**
      - **PZA 1500mg daily**
      - **Moxifloxacin 400mg daily**

CASE – INH/EMB RESISTANCE

TDM RESULTS AS FOLLOWS:

Drug/Dose	2h-level (mcg/ml)	6h-level (mcg/ml)	Reference Cmax
RIF 600 mg	6.8	1.7	**8 - 24**
PZA 1500 mg	31.2	19.6	**20 - 60**
MXF 400 mg	2.1	1.3	**3 - 5**

HOW WOULD YOU ADJUST DAILY DOSES?

A	No dose adjustments necessary
B	↑ Rifampin to 900mg + ↑ Moxifloxacin 800mg daily
C	↑ Rifampin to 1200mg + continue Moxifloxacin 400mg
D	↑ PZA to 3gm, ↓ Rifampin to 450mg, ↑ Moxifloxacin 600mg

CASE – INH/EMB RESISTANCE SUMMARY POINTS

- Moxifloxacin levels
  - Rifampin + Moxifloxacin
    - **Moxifloxacin ↓ ~30% when combined with Rifampin**
    - **Dose adjustments often warranted**

- FQ + Rifampin: C_{max} - dependent effects

- Monitor high FQ doses and QT prolongation

CASE – CAVITARY TB

- 48 yo F (62kg) with pulmonary TB
  - Recent immigrant from Somalia
  - Cavitary lesion in right upper lobe
  - Initiated on daily drug therapy:
    - **Rifampin 600 mg**
    - **Isoniazid 300 mg**
    - **Pyrazinamide 1000 mg**
    - **Ethambutol 800 mg**
- Still smear positive at 3 weeks, TDM ordered

CASE – CAVITARY TB

Drug/Dose	2h-level (mcg/ml)	6h-level (mcg/ml)	Reference Cmax
RIF 600 mg	4.02	6.11	**8 – 24**
INH 300 mg	2.1	Trace	**3 – 6**
PZA 1000 mg	22.2	17.4	**20 – 60**
EMB 800 mg	1.78	1.44	**2 – 6**

HOW WOULD YOU ADJUST DAILY DOSES?

A	↑ RIF to 1200mg + continue INH, PZA, EMB doses
B	↑ INH 600mg + continue RIF, PZA, EMB doses
C	↑ RIF 1200mg + ↑ INH 450mg + ↑ PZA 1500mg + ↑ EMB 1200mg
D	No dose adjustments necessary

CASE – CAVITARY TB

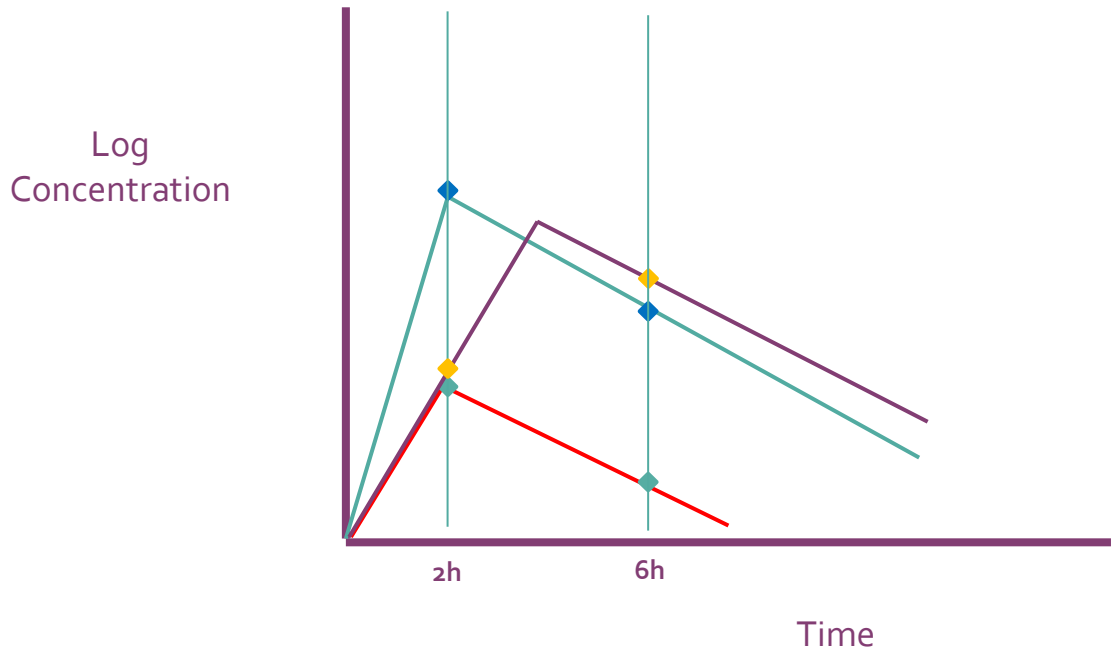
Drug/Dose	2h-level (mcg/ml)	6h-level (mcg/ml)	Reference Cmax
RIF 600 mg	4.02	6.11	**8 – 24**
INH 300 mg	1.42	Trace	**3 – 6**
PZA 1000 mg	22.2	17.4	**20 – 60**
EMB 800 mg	1.78	1.44	**2 – 6**

- INH = poor absorption/low levels → **↑ 450mg**
- RIF = low absorption/low levels + delayed absorption→ **↑ 1200mg**
- EMB = low levels on low dose→ **↑ 1200mg**
- PZA = WNL (low end) on low dose → **↑ 1500mg**

- Recheck levels on new doses

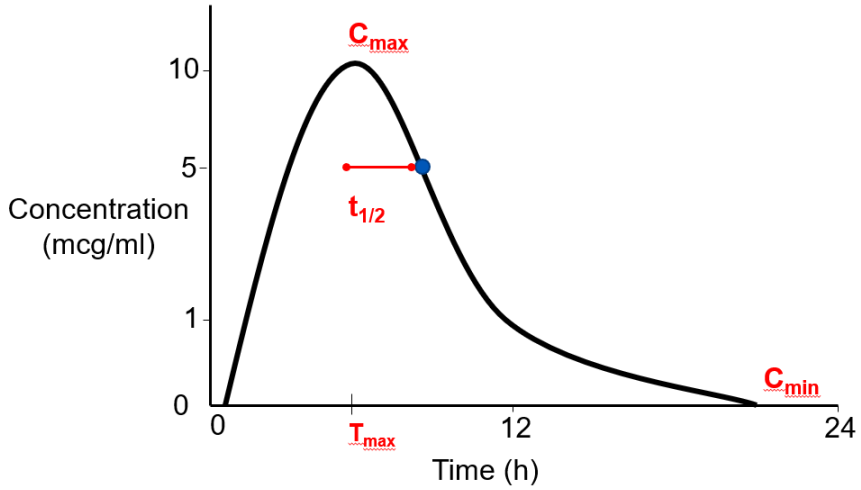
CASE – CAVITARY TB

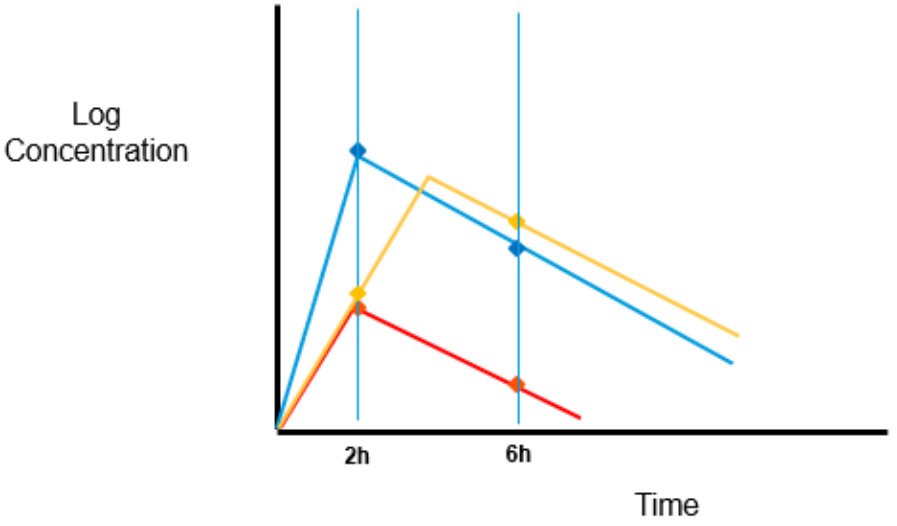
Delayed + Low absorption profile



CASE – CAVITARY TB SUMMARY POINTS

- Delayed absorption
  - Expected T_{max} is later than expected
  - For typical T_{max} ~2h
    - 6h level > 2h level
- Malabsorption
  - 2-hour C_{max} is lower than expected
  - 6h level lower than 2h level
    - Reflecting anticipated clearance





Daily dosing	EMB	PZA
56-75kg	1200 mg	1500 mg

AMINOGLYCOSIDE TDM

4

CASE – MDR TB

18 YO (71KG) M WITH MDR-TB
NORMAL RENAL/HEPATIC FUNCTION
NO OTHER MEDICATIONS

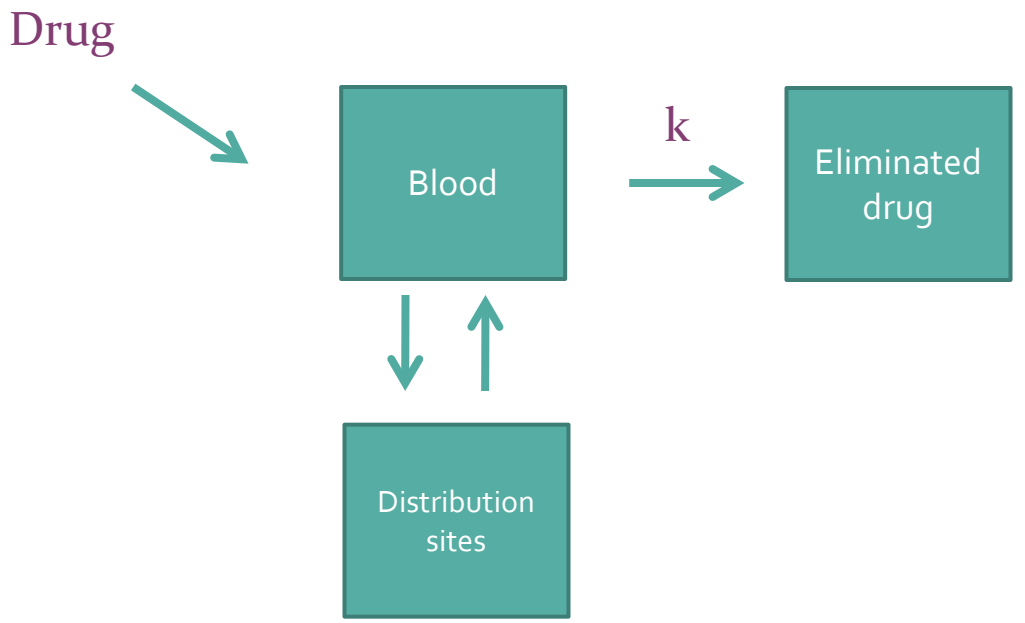
- **Oral**
  - Moxifloxacin 400 mg
  - Clofazimine 100 mg
  - Linezolid 600 mg
  - Ethambutol 1200 mg
- **IV**
  - Amikacin 1100 mg (~15mg/kg)

HOW SHOULD YOU ASSESS BLOOD LEVELS?

A	2h and 6h after oral doses
B	AMK trough + 2h/6h post oral doses
C	LZD trough + 2h/6h post oral dose + 2h/6h after END of AMK infusion
D	LZD trough + AMK trough + 2h/6h post oral doses

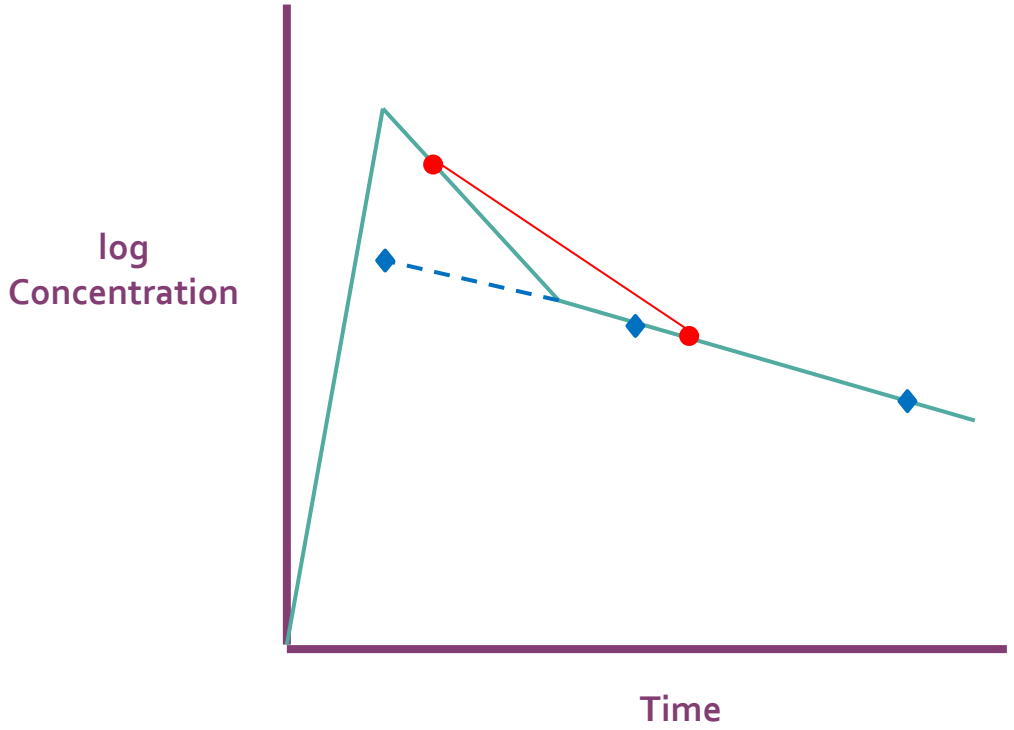
DISTRIBUTION: ONE VS TWO-COMPARTMENT

$$C_1 = C_2 \times e^{(k \times \blacktriangle t)}$$



$$C = \frac{D(\alpha - k_{21})}{V_{D_1}(\alpha - \beta)} e^{-\alpha t} + \frac{D(k_{21} - \beta)}{V_{D_1}(\alpha - \beta)} e^{-\beta t}$$

AMINOGLYCOSIDE CONCENTRATION-TIME PROFILE



AMINOGLYCOSIDE TDM IN TB

- TDM Strategy
  - Post-infusion levels → Confirm dose
    - C_{max} = bacterial effect
  - Dose confirmation → weekly trough
    - Clearance confirmation
    - Toxicity mitigation

1) Aminoglycosides blood levels:
   - 2 hours + 6 hours
   - After **END** of infusion

2) Calculate C_{max}
   - Back-extrapolation
   - Dose adjust to target

3) Aminoglycoside C_{max} goals:
   - 15 mg/kg : **35-45 mcg/ml**
   - 25 mg/kg: **65-80 mcg/ml**

AMINOGLYCOSIDE ASSESSMENT REASONS

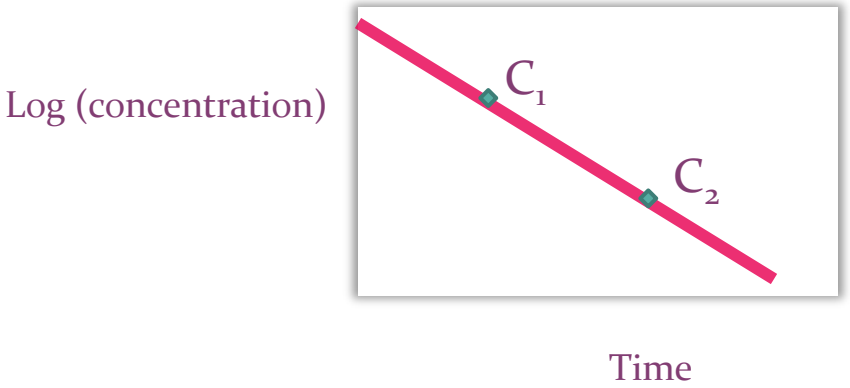
- Why wait 2 hours after an IV dose?
  - **Allows re-distribution and blood-tissue equilibrium**
  - **Prevents artificial inflation of clearance calculation**
  - **Allows 1-compartment model and one-compartment equations**

- Why 2 levels if absorption not an issue?
  - Both required for elimination rate constant (k) calculation
    - **Measure of body's ability to clear drug**
    - **Determines half-life (0.693/k)**
    - **Needed to back-extrapolation Cmax (end of infusion)**

CASE -MDR TB

Step 1: solve for k

$C_1 = C_2 \times e^{(k \times \blacktriangle t)}$ → $k = [\ln (C_1/C_2)]/\blacktriangle t$



- **Elimination rate constant (k)**
  - First order rate constant for calculating drug elimination
  - 'slope' of our log-scale: Concentration - Time profile
  - k determines half-life
    - Half-life = 0.693/k
      - If k = 0.331 h^{-1}, half life = 3h

CASE – MDR TB

Drug/Dose	Trough (mcg/ml)	2h-level (mcg/ml)	6h-level (mcg/ml)	Reference Cmax
MXF 400 mg	-	4.1	2.8	**3 – 5**
CFZ 100 mg	-	1.3	0.7	**0.5 – 2.0**
EMB 1200 mg	-	3.1	2.2	**2 – 6**
LZD 600mg	2.9	28.1	17.6	**12 – 26**
AMK 1100 mg IV	-	20	5	**35 – 45**

HOW SHOULD YOU ADJUST ORAL TB DOSES?

A	No dose adjustment required
B	↓ MXF to 200mg
C	↑ CFZ to 200mg
D	↓ LZD to 300mg daily

CASE – MDR TB

- Oral TDM assessments:
  - MXF, CFZ, and EMB doses appropriate
  - Linezolid
    - 2h level elevated
    - Troughs >2 (associated with toxicity)
    - **Reduce LZD to 300mg daily**
- **What adjustments do you need to make to Amikacin?**

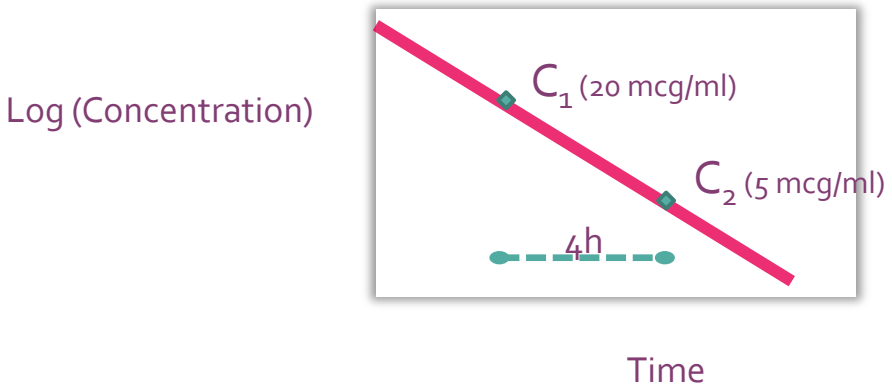
Drug/Dose	Trough (mcg/ml)	2h-level (mcg/ml)	6h-level (mcg/ml)	Reference Cmax
MXF 400 mg	-	4.1	2.8	**3 – 5**
CFZ 100 mg	-	1.3	0.7	**0.5 – 2.0**
EMB 1200 mg	-	3.1	2.2	**2 – 6**
LZD 600mg	2.9	28.1	17.6	**12 – 26**

CALCULATE THE ELIMINATION RATE CONSTANT

Drug/Dose	Trough (mcg/ml)	2h-level (mcg/ml)	6h-level (mcg/ml)	Reference Cmax
AMK 1100 mg IV	-	20	5	**35 – 45**

- <u>Step 1: solve for K</u>

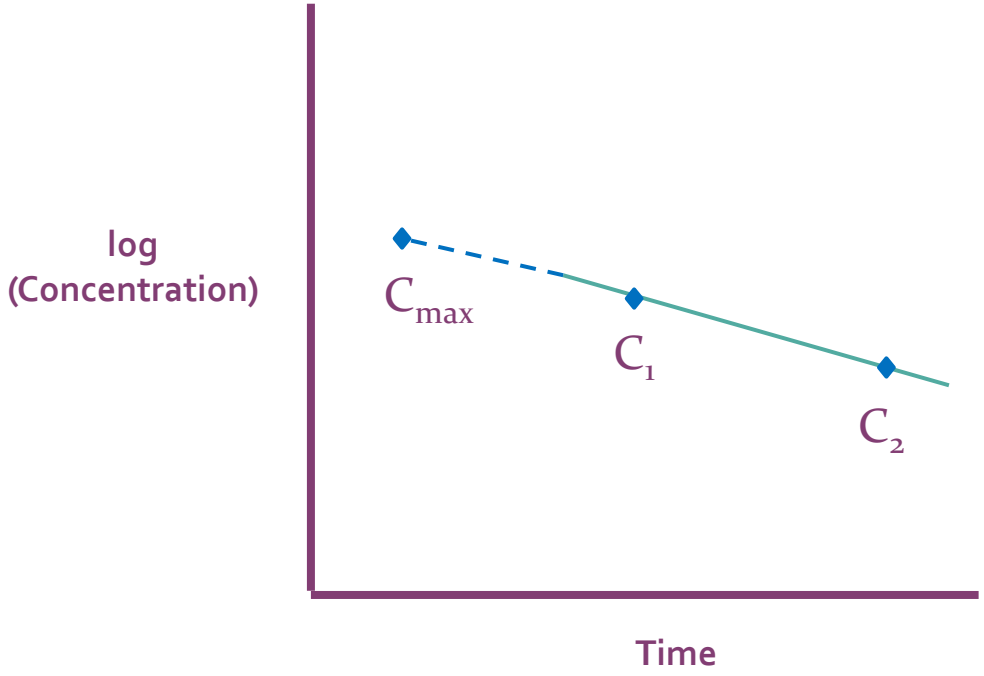
- $k = [\ln (C_1/C_2)]/\blacktriangle t$
- $k = [\ln (20/5)]/4h = 0.346\ h^{-1}$
- Half life = 0.693/k = 2 hours



CALCULATING THE C_{MAX}

Step 2: Use k to calculate C_{max}

- C_{max} = Concentration (end of infusion)
- $C_{max} = C_1 \times e^{(k \times \blacktriangle t)}$
- $C_{max} = 20 \times e^{(0.346 \times 2)} =$ **40 mcg/ml**



- AMK 1100mg in Cmax goal range (35-45 mcg/ml)
  - **Continue AMK 1100mg daily**
  - Weekly trough/SCr for toxicity monitoring

CASE – MDR TB: SUMMARY POINTS

- Linezolid trough levels monitored for toxicity
- Do not draw aminoglycoside levels during distribution phase
    - Artificially inflated
    - Unable to determine appropriate clearance
- Aminoglycoside levels (Amikacin, Streptomycin, Kanamycin)
    - Draw 2 post-distribution levels
    - 2h and 6h after **END** of infusion
    - Calculate k (determines half-life and C_{max})
- Aminoglycoside goal range for calculated C_{max}
    - 15 mg/kg: **35 - 45 mcg/ml**
    - 25 mg/kg: **65 - 80 mcg/ml**

HELPFUL REFERENCES

- Maranchik NF, Peloquin CA. Role of therapeutic drug monitoring in the treatment of multidrug resistant TB. Under Review
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QUESTIONS & ANSWERS

THANK YOU!