



Optimizing TB Therapy: Therapeutic Drug Monitoring

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Disclosure:

No relevant financial disclosures

Off-label mention for TB treatment:

- Clofazimine
- Levofloxacin
- Moxifloxacin
- Rifabutin
- Amikacin

Learning Objectives

- Review key principles of therapeutic drug monitoring (TDM)
- Identify TB cases appropriate for TDM
- Interpret TDM results and adjust drug therapy appropriately

Therapeutic drug monitoring (TDM)

WHAT, WHY, AND WHO

What is Therapeutic Drug Monitoring?

- Measuring drugs levels
 - Usually blood levels (surrogate marker)
- Designated intervals
- Target concentrations/range
- Optimize dosage regimen



Why perform drug levels during TB management?

Efficacy target

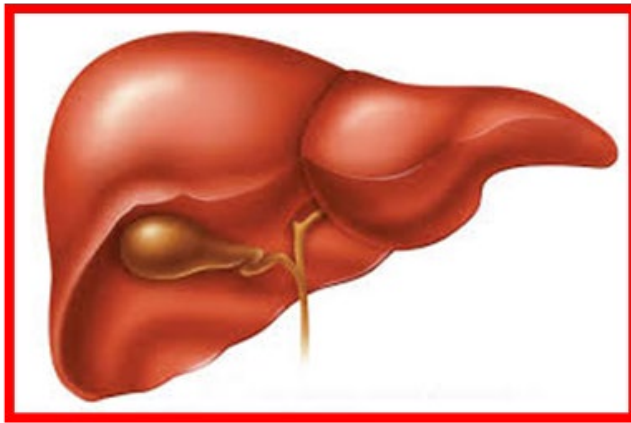
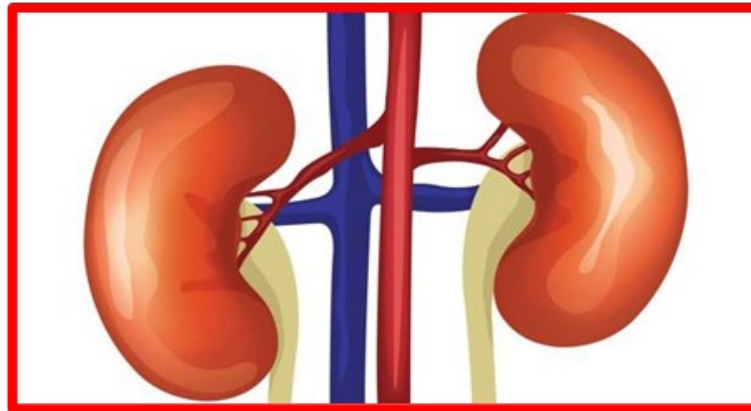
Minimize toxicity

Compliance
measure

Confirm
absorption

Assess
presence or
degree of drug
interaction

Same TB dose for everyone?



TDM for whom?

- Slow responders
- Extremes of weight
- Impaired drug clearance
 - Kidney function
 - Liver function
- Concerning drug interactions
- Malabsorption potential
- Elevated drug toxicity risk



Summary

- **Blood level assessment:**
 - Informs drug exposure
- **Standard TB drug doses**
 - Anticipated exposure
 - Expected outcome
- **Outliers exist**



- **TDM**
 - Patient-specific drug exposure information
 - Individualize Treatment
 - May enhance TB outcome
- **TDM candidates**
 - Slow TB response
 - High/low exposure potential



Which patient scenario would least likely see benefit from serum drug level assessment of oral TB therapy?

Rifabutin (CYP3A4 substrate) + Darunavir/Ritonavir (CYP3A4 inhibitors)

0%

Chronic liver disease (Child's Pugh C), ascites, and low body weight (45kg)

0%

Non-cavitary, drug-sensitive TB. 70kg. Otherwise, healthy

0%

MDR TB with history of small bowel resection

0%



##/##

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Results slide

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RESULTS SLIDE

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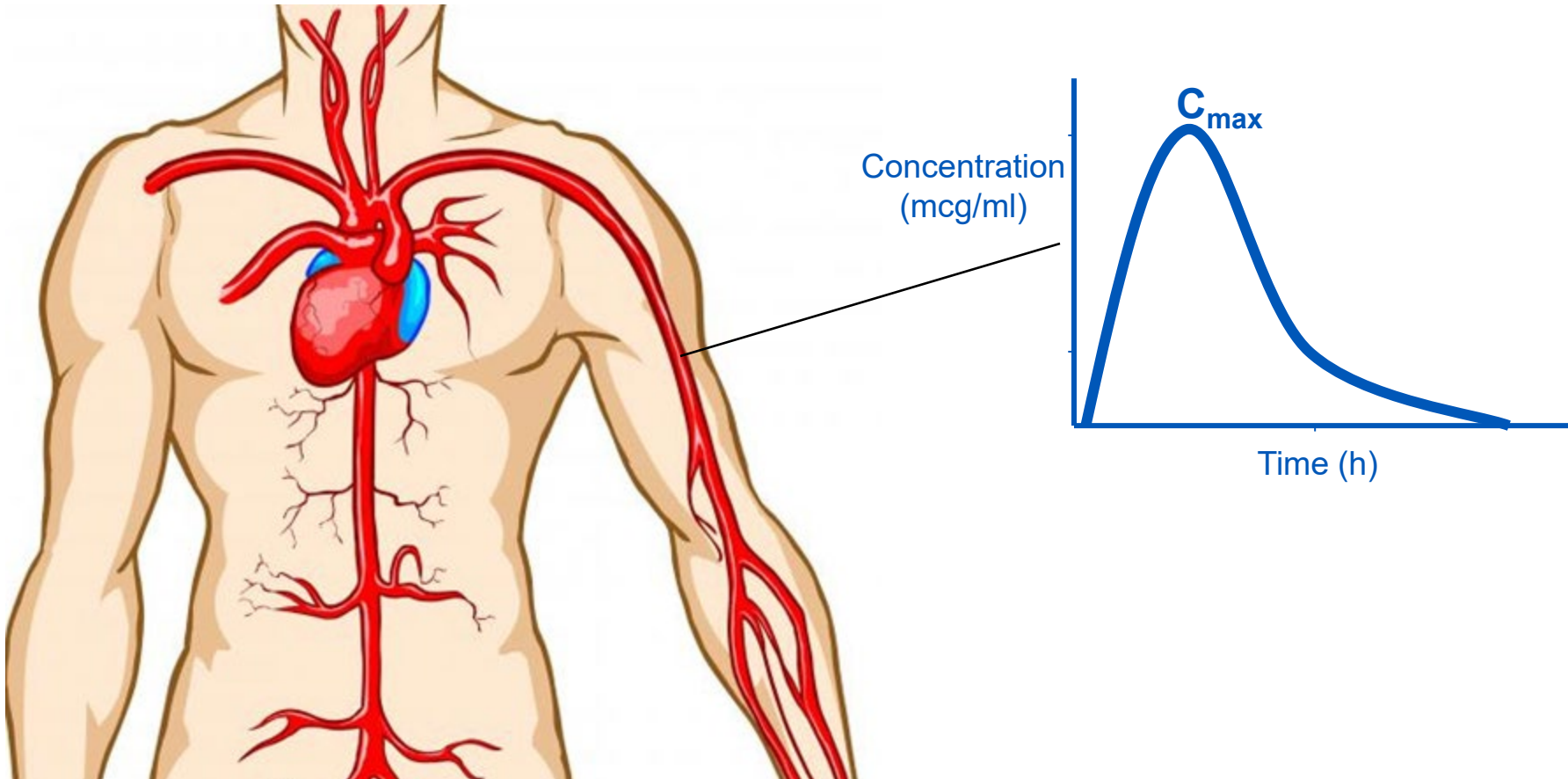
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D	MDR TB with history of small bowel resection



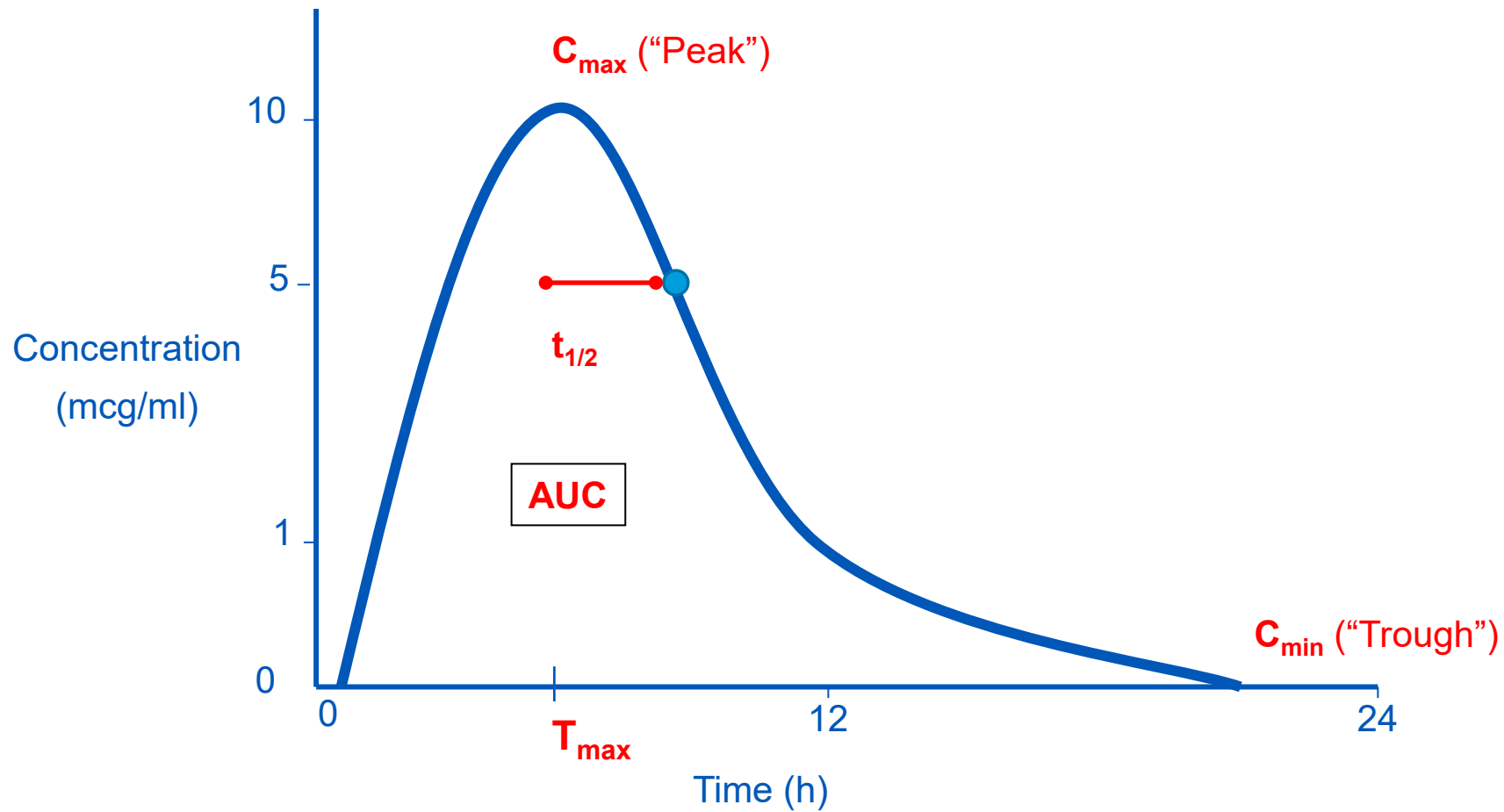
How to perform TDM?



Blood levels = surrogate marker

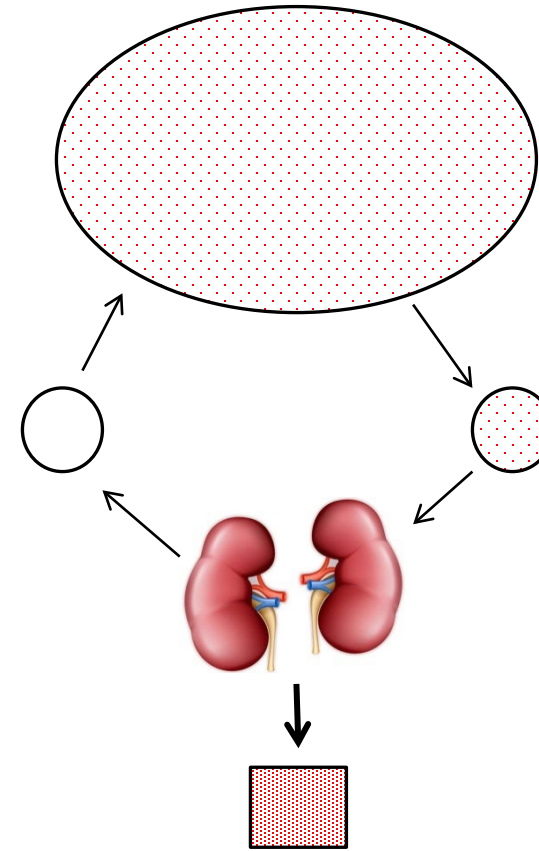
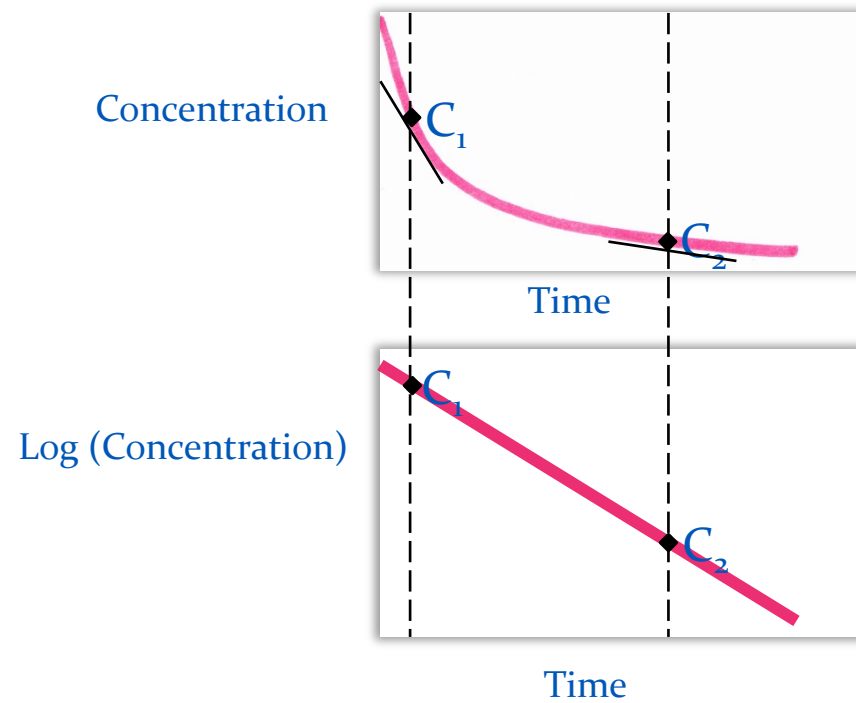


Pharmacokinetic (PK) terms



AUC = Area under the curve

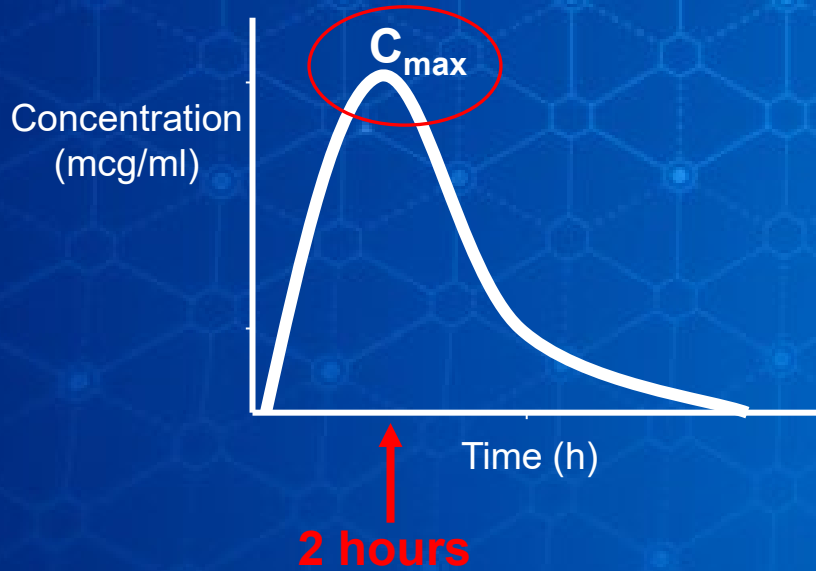
First Order Kinetics



When to draw blood for oral TB TDM

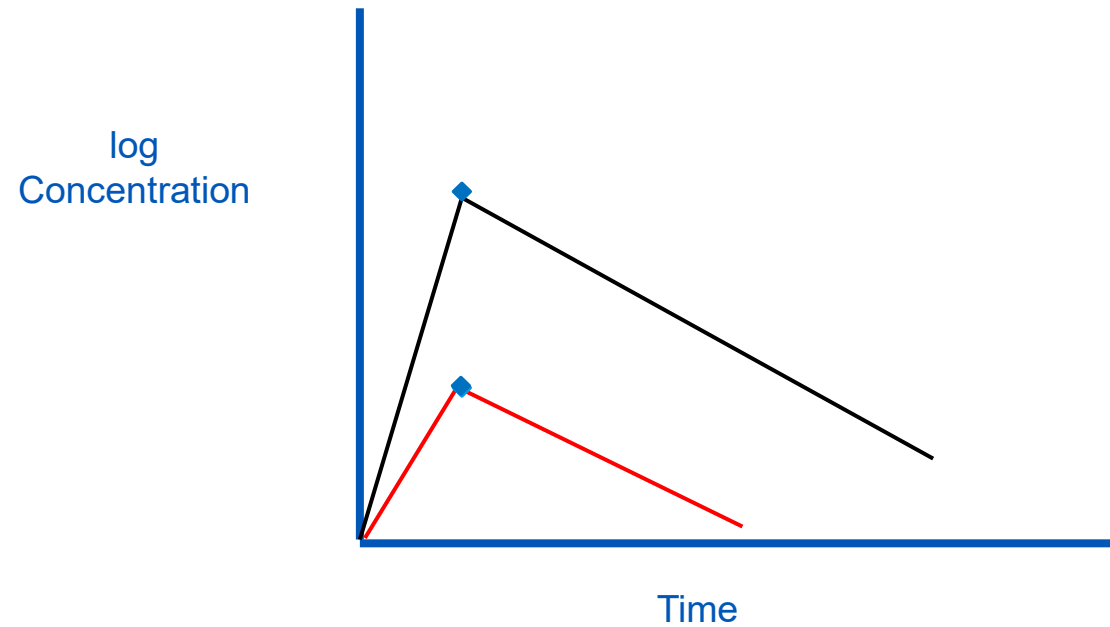


Peak ($C_{\max}$) Blood draws

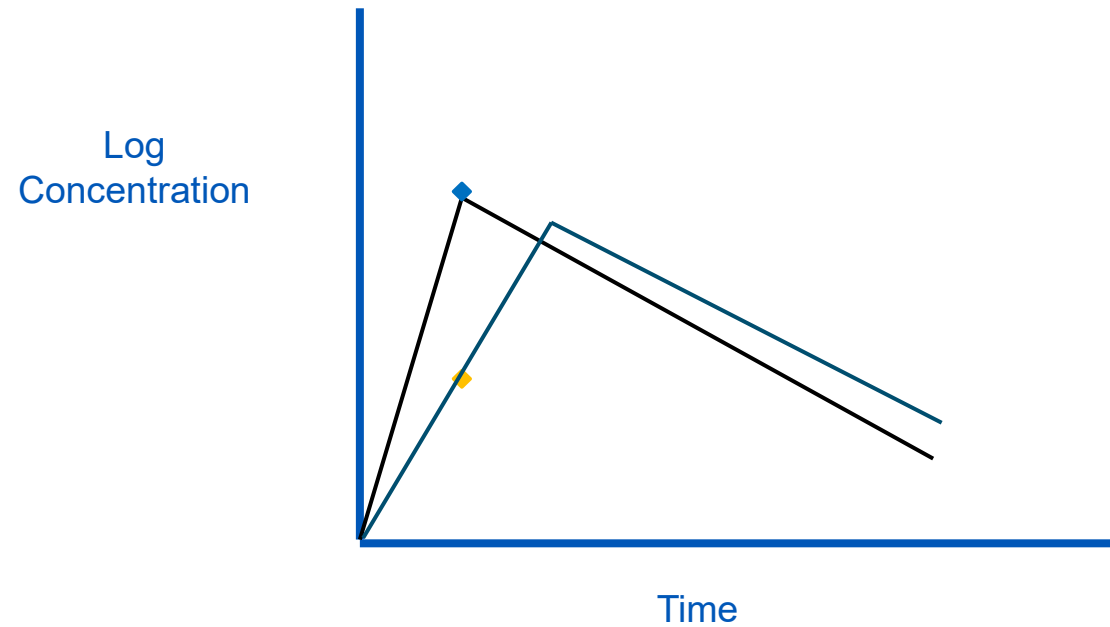


- **TWO-hour blood sample**
 - 2 hours after oral dose
 - Approximates “peak”
 - For many oral TB drugs
 - $T_{\max}$ close to 2 hours
 - Absorption information
- **Trough levels?**
 - Short half-life TB drugs
 - Often below assay detection limit

Single assessment- malabsorption



Single assessment – Delayed Absorption



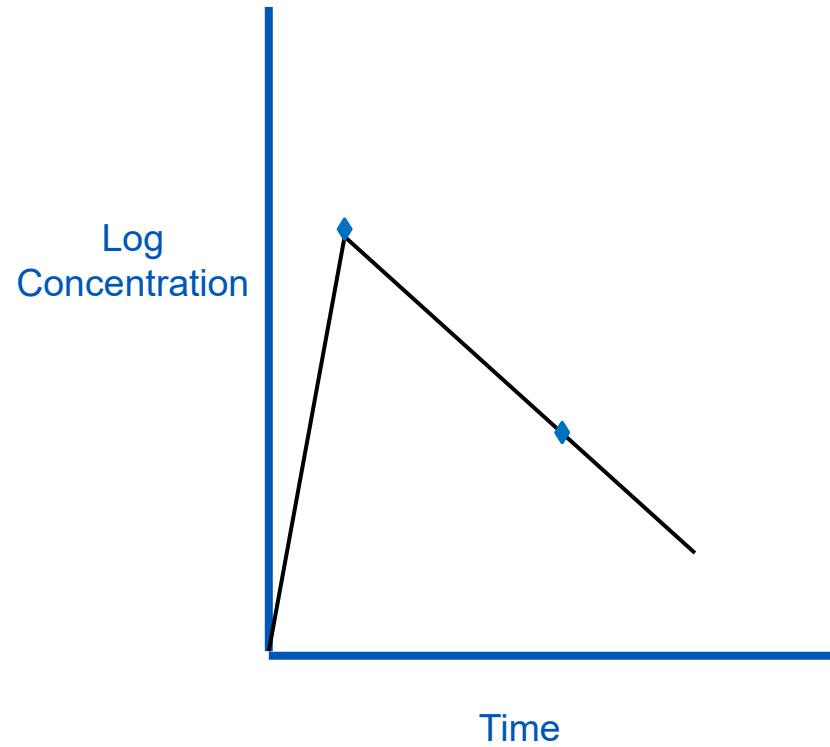
Two Assessments = Improved Information

- **Adding a 6-hour post oral dose blood sample**
 - Rate + extent of absorption
 - Elimination/drug clearance
 - Malabsorption vs delayed absorption
- **Preferred approach for most oral TB therapies**
 - Two blood level assessments
 - 2-hours and 6-hours after oral dose

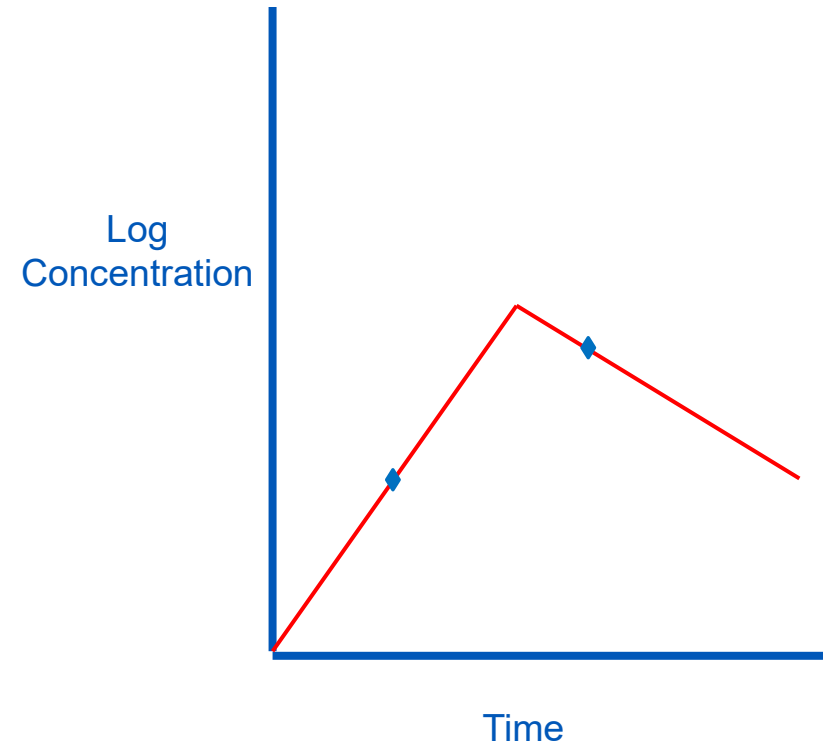


2-hour + 6-hour post oral dose levels

Drug Clearance information



Slow/Delayed absorption



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

Summary - TDM approach

- Dual blood level assessment
 - 2-hour and 6-hour post oral doses for most
- Consider pharmacokinetics of specific drugs
 - Later peak (~5-6h): BDQ, PTM, RPT, PAS
 - Trough level: BDQ, PTM, LZD, RPT



Rifampin, isoniazid, pyrazinamide and ethambutol administered at 0800 When should blood levels be drawn?

0730 and 1200

0%

0800 and 1000

0%

1000 and 1400

0%

0900 and 1100

0%



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Results slide

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0900 and 1100

##.##%

RESULTS SLIDE

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

Case – INH/EMB Resistance



- 31 yo F (74 kg) from DRC (Congo)
 - Bilateral cavitary pulmonary TB
 - Normal kidney/liver function
 - No comorbidities
 - Resistance to INH and EMB
 - Regimen:
 - **Rifampin 600 mg daily**
 - **PZA 1500mg daily**
 - **Moxifloxacin 400mg daily**



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 therapy?

No dose adjustments necessary

0%

^B
↑ Rifampin to 900mg + ↑ Moxifloxacin 800mg daily

0%

↑ Rifampin to 1200mg + continue Moxifloxacin 400mg

0%

↑ PZA to 3gm, ↓ Rifampin to 450mg, ↑ Moxifloxacin 600mg

0%



0

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Preparing Results

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RESULTS SLIDE

TDM results

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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

Summary Points



- Rifampin + Moxifloxacin
 - Moxifloxacin ↓ ~30%
 - Dose adjustments can be warranted
- Fluoroquinolones + Rifampin
 - $C_{\max}$ - dependent bactericidal effects
- High fluoroquinolone doses
 - Monitor for QT prolongation

Case – Cavitory TB

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





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 therapy?

↑ RIF to 1200mg + continue INH, PZA, EMB doses

0%

↑ INH 600mg + continue RIF, PZA, EMB doses

0%

↑ RIF 1200mg + ↑ INH 450mg + ↑ PZA 1500mg + ↑ EMB 1200mg

0%

No dose adjustments necessary

0%



0

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RESULTS SLIDE

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How would you adjust therapy?

A	↑ RIF to 1200mg + continue INH, PZA, EMB doses
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C	↑ RIF 1200mg + ↑ INH 450mg + ↑ PZA 1500mg + ↑ EMB 1200mg
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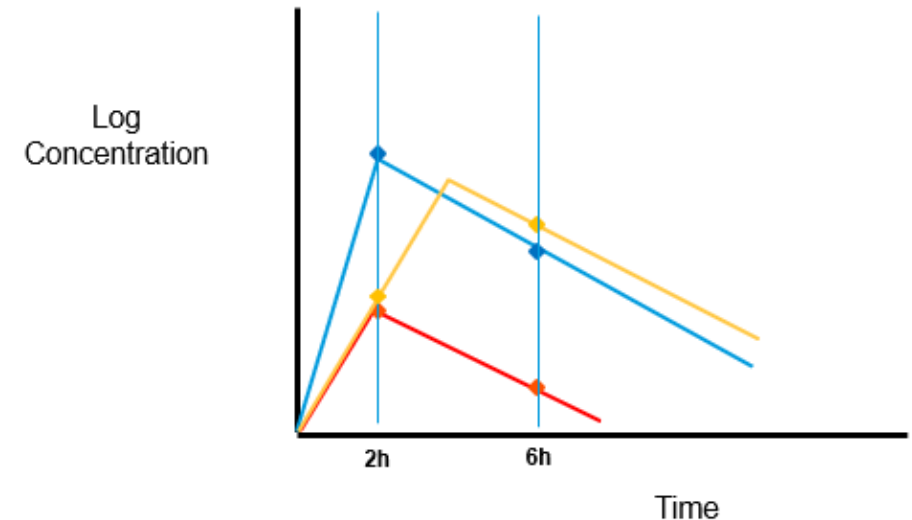
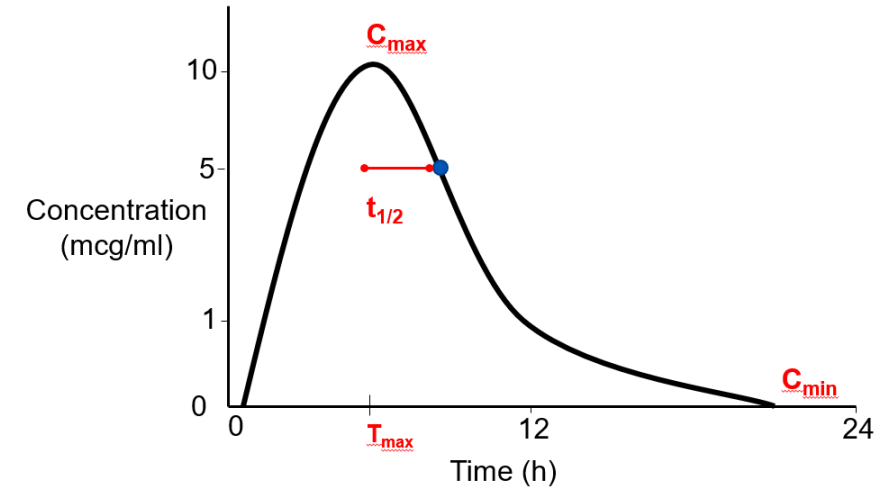
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- RIF = low absorption/low levels + delayed absorption → ↑ 1200mg
- INH = poor absorption/low levels → ↑ 450mg
- PZA = WNL (low end) on low dose → ↑ 1500mg
- EMB = low levels on low dose → ↑ 1200mg
- Recheck levels on new doses

CASE – CAVITARY TB SUMMARY POINTS

- Delayed absorption
 - Expected T_{max} is later than expected
 - For typical $T_{max} \sim 2h$
 - 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

Helpful References

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Questions and Answers





Thank you