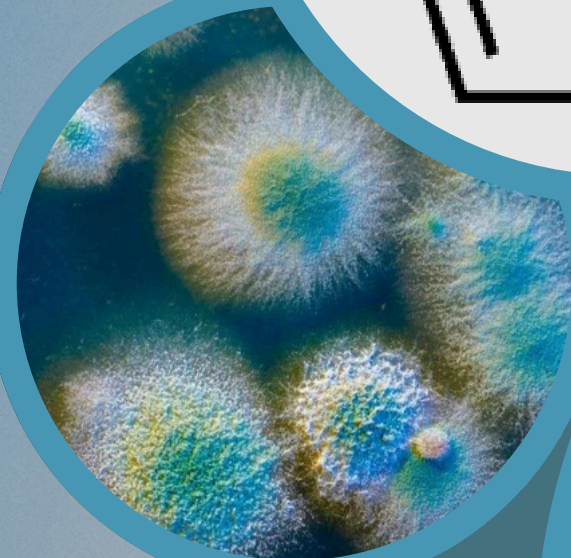
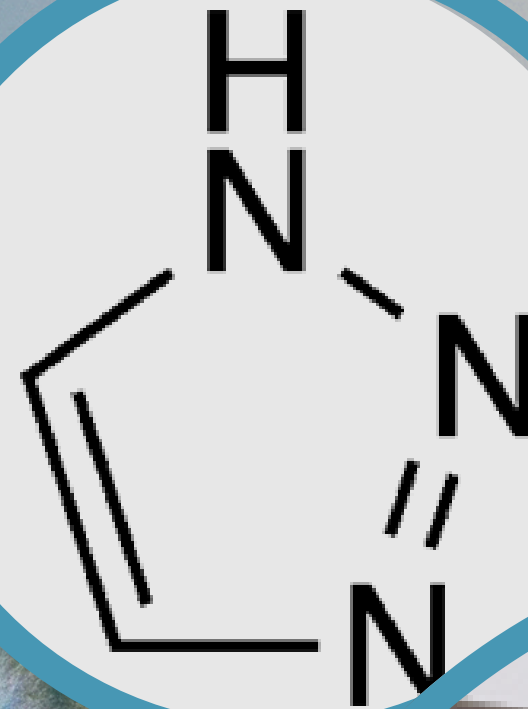


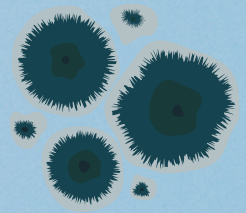
THERAPEUTIC DRUG MONITORING TRIAZOLES

*Sampling time :
Why does it matter?*

**By: WONG E-JINQ
AMS PHARMACIST**

9 APR 2025



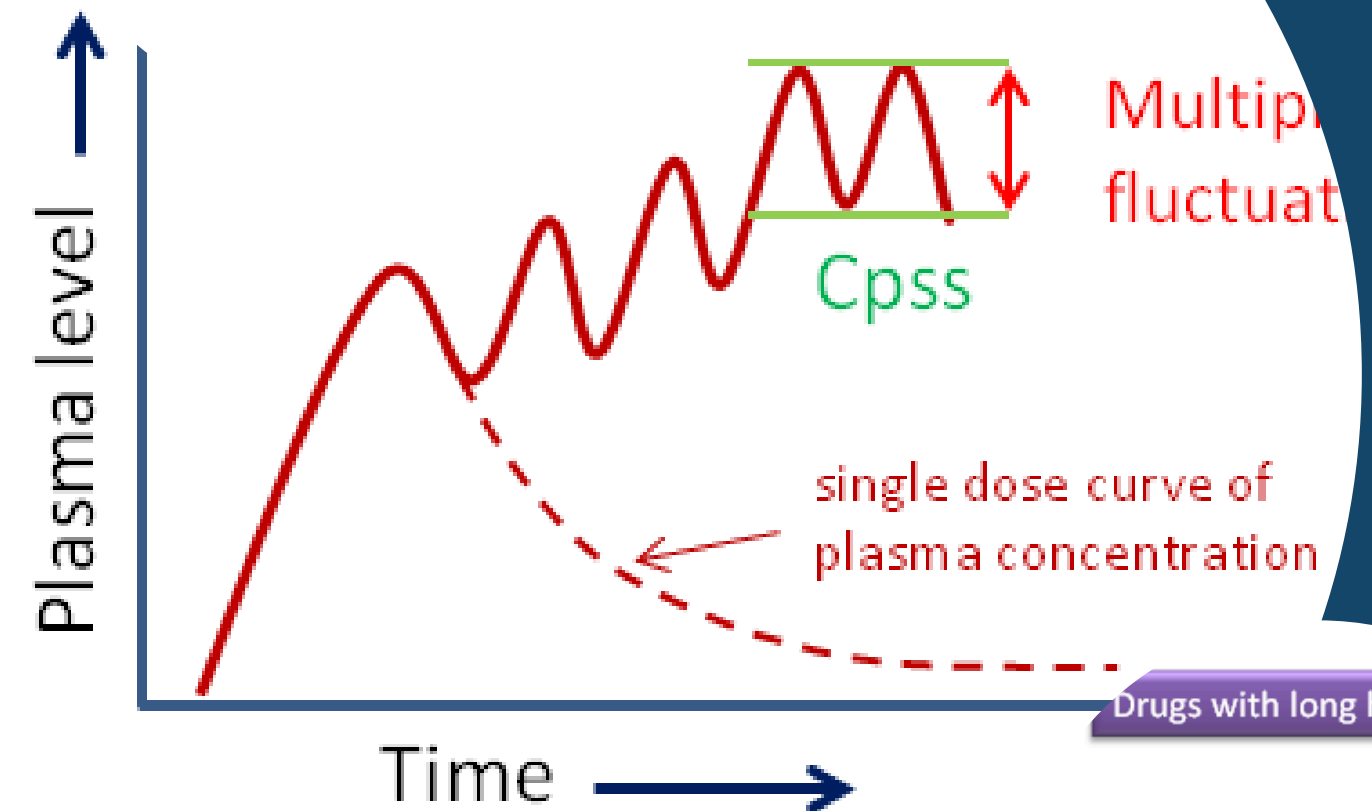
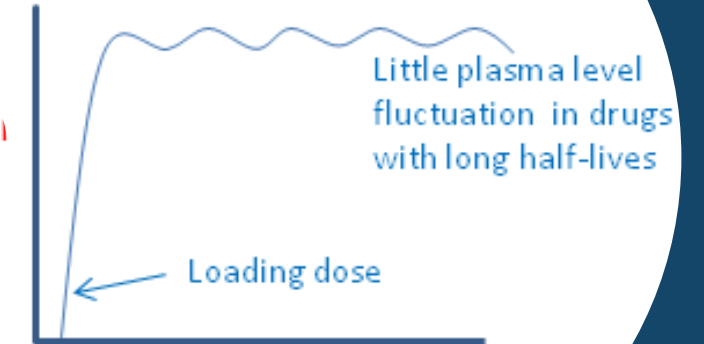
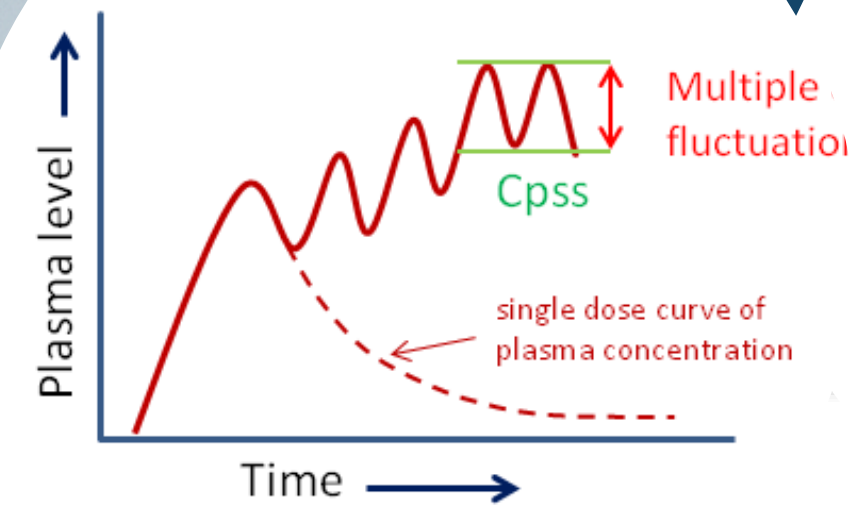


TDM Triazoles

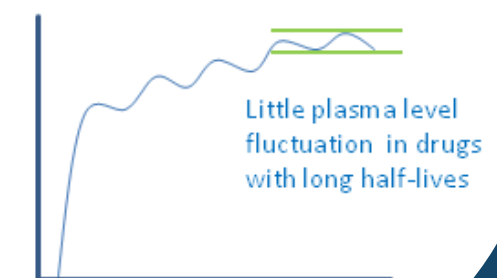
INTRODUCTION

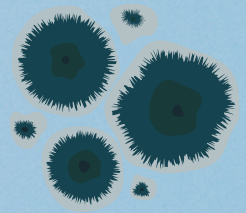
- Many antifungals exhibit **narrow therapeutic indices**, meaning the concentration difference between efficacy and toxicity is small.
- **Inter-patient pharmacokinetic variability** is significant due to factors like genetics, age, organ function, and drug interactions.

Drugs with short half-lives



Drugs with long half-lives



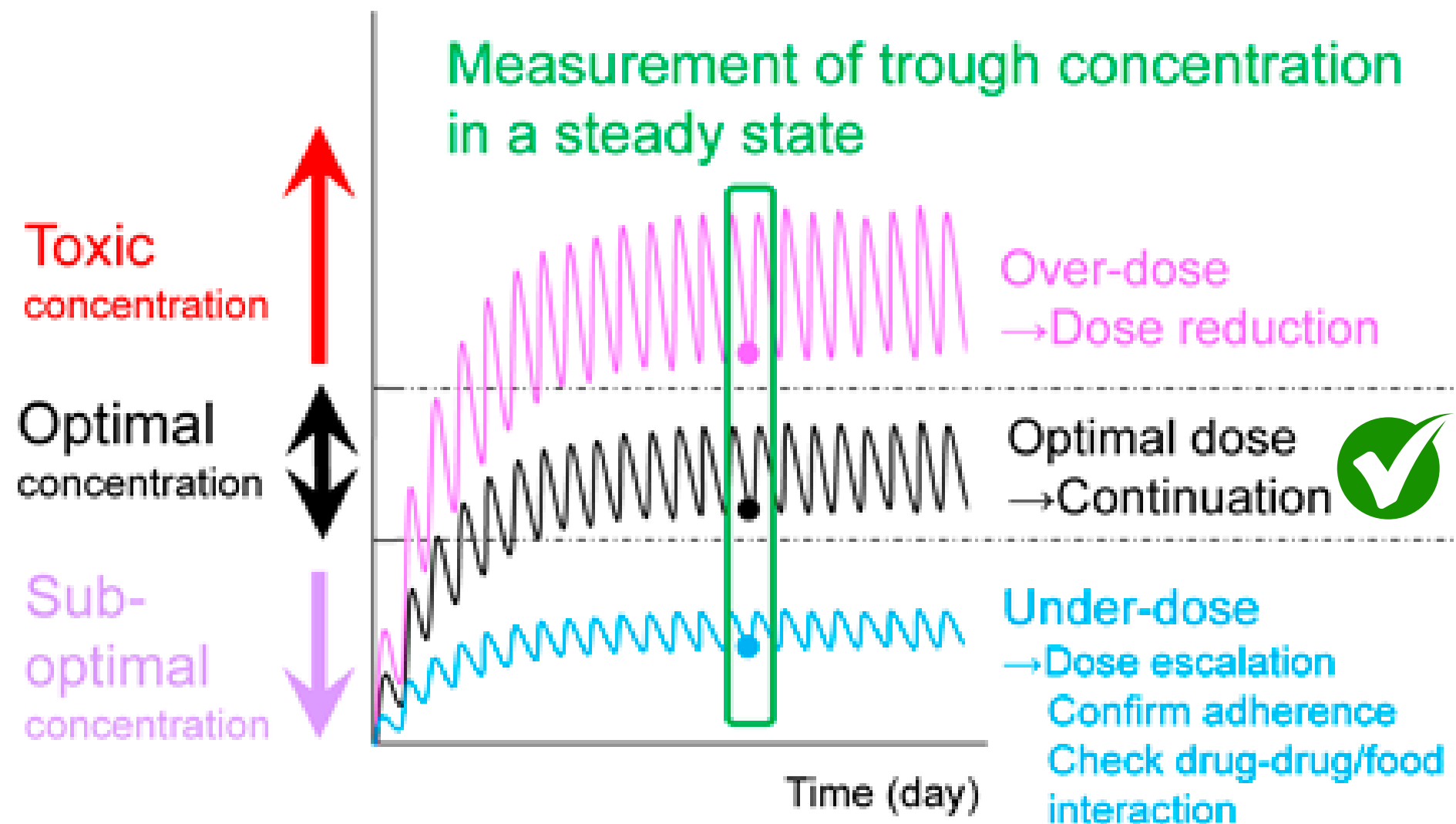


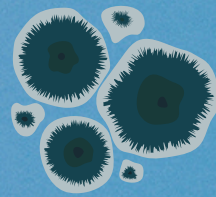
TDM Triazoles

INTRODUCTION

- Subtherapeutic levels can lead to **treatment failure and resistance** development, while **supratherapeutic levels increase the risk of toxicity**.
- **TDM helps individualize dosing.**
- **Thus, maximizing efficacy, minimizing toxicity and prevent resistance.**

Dose optimization of oral multi-kinase inhibitors using therapeutic drug monitoring





Triazoles

TYPES OF TRIAZOLES ANTIFUNGAL

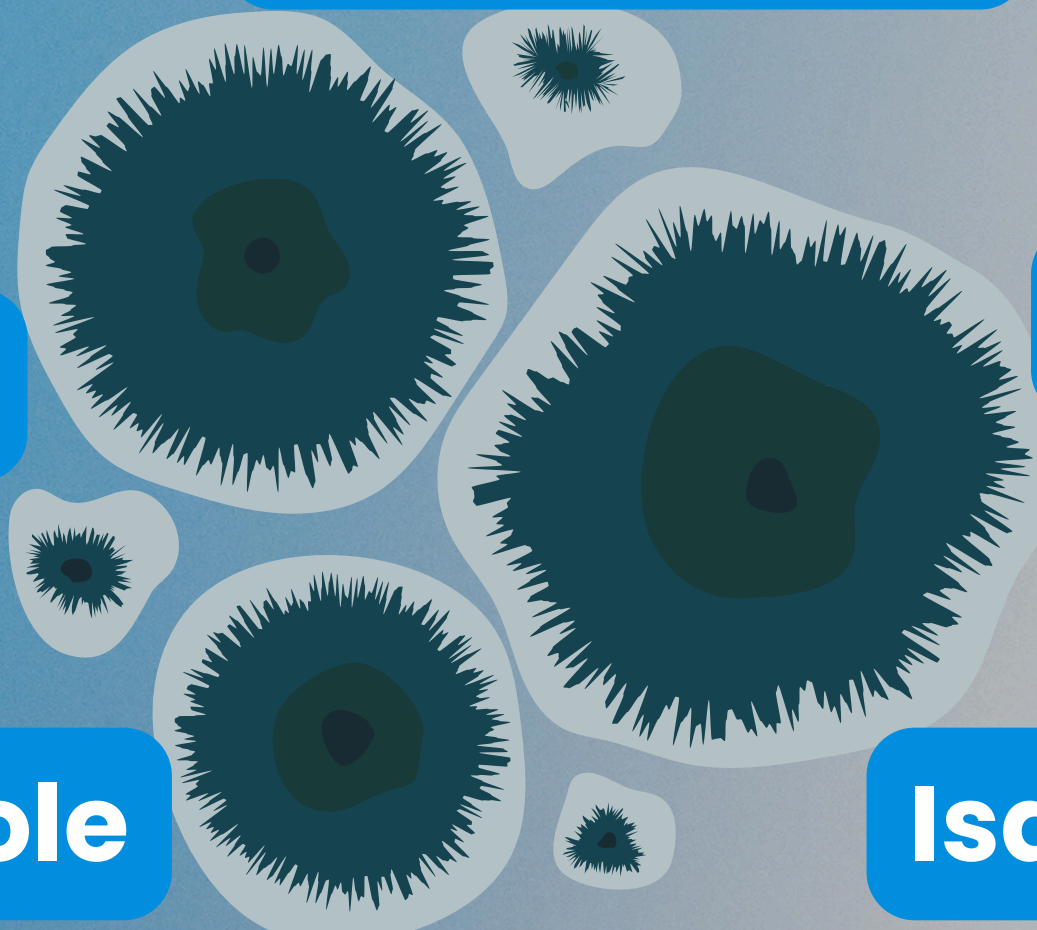
Voriconazole

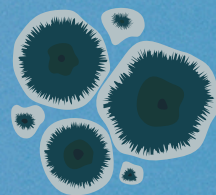
Itraconazole

Posaconazole

Fluconazole

Isavuconazole



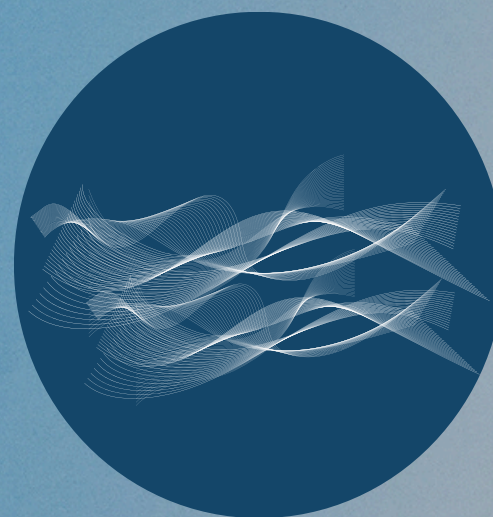


Triazoles

LIFE-TREATENING FUNGAL INFECTIONS



Aspergillosis



Fusariosis



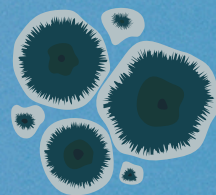
**Cryptococcal
meningitis**



Mucormycosis



Candidaemia



Triazoles

COMMON ADVERSE EFFECT



Hepatotoxicity



**Visual
Disturbance**



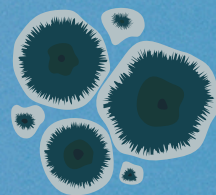
**Neurological
toxicity**



GI upset

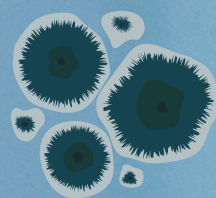


Skin Reactions



Triazoles

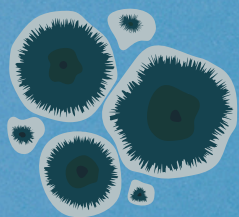
**WHAT ARE THE DIFFERENCE
OF THIS ASSAY WITH
PREVIOUS?**



Triazoles

IMMUNOFLUORESCENCE (IF) VS LIQUID CHROMATOGRAPHY- MASS SPECTROMETRY (LCMS)

| Criteria | Immunofluorescence | Liquid Chromatography-Mass Spectrometry (LC-MS) |
|---|--|--|
| Method Used to Analyze Sample | Antibody binding to target drug/antigen, followed by fluorescence detection. | Separation of compounds by liquid chromatography followed by mass spectrometric detection. |
| Turnaround Time | Typically 1-3 hours | Generally 2-4 hours (longer if extensive sample prep is required) |
| Equipment Cost & Operational Complexity | Low – fluorescent microscope or plate reader required – kit-based and user-friendly | High – requires specialized instruments and trained personnel – requires technical expertise for method development and validation |
| Sensitivity & Specificity | Moderate – suitable for higher concentration drugs Lower – possible cross-reactivity with similar molecules | High – capable of detecting trace levels and metabolites Very high – distinguishes between structurally similar compounds and metabolites |
| | Rapid, cost-effective, Less sensitive, Less specific, Limited by drug reagent availability | Slower, Costly, High accuracy & specificity, excellent for polypharmacy /complex TDM |



Why TDM Triazoles is important?

Non-linear pharmacokinetics

01

Triazoles exhibit non-linear pharmacokinetics, meaning that dose increases do not result in proportional increases in drug concentrations. This makes TDM crucial for this class.

Drug-drug interactions

02

Triazoles are susceptible to significant drug-drug interactions, which can greatly alter their serum concentrations and affect both efficacy and safety. TDM is essential to manage these interactions.

Genetic polymorphisms

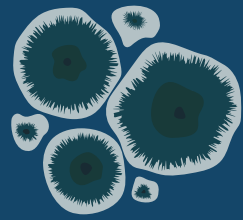
03

The risk of toxicity and subtherapeutic levels is increased in patients with specific genetic polymorphisms affecting drug metabolism. TDM can help to account for this inter-individual variability.

Variable bioavailability

04

The bioavailability of oral triazoles can be highly variable, depending on the specific drug, formulation, and patient-specific factors (e.g., food intake, gastric pH). TDM helps to ensure adequate drug exposure.



TDM Triazoles

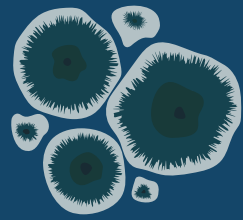
NON-LINEAR PHARMACOKINETIC

- Exhibit saturable and non-linear PK
- Relationship between dose and serum concentration is not directly proportionate

- Complex dosing adjustment

Example

- Increasing 50mg in individual A at serum concentration 1 and concentration 2 will be resulting in different increment in their serum concentration.
- TDM provide monitoring in reassurance after dosing adjustment been made.



TDM Triazoles

GENETIC POLYMORPHISM

The risk of toxicity and subtherapeutic levels is increased in patients with specific genetic polymorphisms affecting drug metabolism.

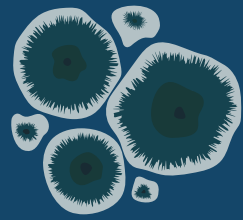
Blanco-Dorado S, Maroñas O, Latorre-Pellicer A, et al. A. Impact of CYP2C19 Genotype and Drug Interactions on Voriconazole Plasma Concentrations: A Spain Pharmacogenetic-Pharmacokinetic Prospective Multicenter Study. *Pharmacotherapy*. 2020 Jan;40(1):17-25. doi: 10.1002/phar.2351. PMID: 31782536.

Dean L. Voriconazole Therapy and CYP2C19 Genotype. 2019 Dec 27. In: Pratt VM, Scott SA, Pirmohamed M, et al., editors. *Medical Genetics Summaries* [Internet]. Bethesda (MD): National Center for Biotechnology Information (US); 2012-. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK552035/>

- **Caucasians and Blacks, the prevalence of poor metabolizers is 3 to 5%**
- **Average, 4-fold higher voriconazole exposure (AUC_τ) than their homozygous normal metabolizer counterparts**

Example

- Voriconazole metabolism significantly affected by Polymorphisms in CYP2C19 in both single dose and multiple dosing patients.
- Although Isavuconazole is a substrate of CYP3A4, but variants alleles are unlikely to affect it's clearance.



TDM Triazoles

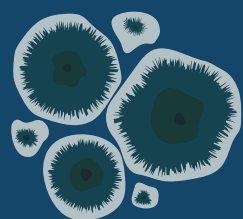
GENETIC POLYMORPHISM

- Polymorphisms in CYP2C9 and CYP3A4
- Polymorphism of the transporter gene ABCB1-rs1045642

- **Metabolized in the liver by CYP3A4, CYP2C9 and CYP2C19**
- **Polymorphisms in CYP2C19, but not CYP3A5 or CYP2C9 have been reported to affect its pharmacokinetic**

Example

- In both Western and Chinese patients, CYP2C19 polymorphism shows significant impact on voriconazole pharmacokinetics.
- CYP2C9, CYP3A4, and FMO3 genetic polymorphisms do not show significant difference in voriconazole pharmacokinetics



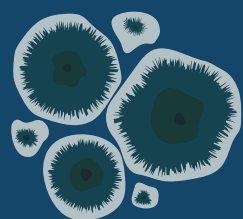
TDM Triazoles

GENETIC POLYMORPHISM

Table 2 Inhibitory potency of antifungal agents on selected CYP enzymes^{26,28–34}

| | CYP2C9 | | CYP2C19 | | CYP3A4 | |
|---------------|-----------|------------|-----------|------------|-----------|------------|
| | Substrate | Inhibition | Substrate | Inhibition | Substrate | Inhibition |
| Itraconazole | 0 | 0 | 0 | 0 | √ | +++ |
| Posaconazole | 0 | 0 | 0 | 0 | 0 | +++ |
| Voriconazole | √ | + | √ | ++ | √ | +++ |
| Fluconazole | 0 | ++ | 0 | +++ | 0 | ++ (#) |
| Isavuconazole | 0 | 0 | 0 | 0 | √ | ++ |
| Caspofungin | 0 | 0 | 0 | 0 | 0 | 0 |
| Anidulafungin | 0 | 0 | 0 | 0 | 0 | 0 |
| Micafungin | 0 | 0 | 0 | 0 | 0 | 0 |
| Olorofim | * | * | * | * | √ | + |
| Rezafungin | 0 | 0 | 0 | 0 | 0 | 0 |
| Ibrexafungerp | * | * | * | * | √ | + |

+, weak; ++, moderate; +++, strong; classification based upon US Food and Drug Administration guidance³⁵; √, CYP substrate; *, still being evaluated in clinical trials with limited published data available; #, dose ≥200 mg.

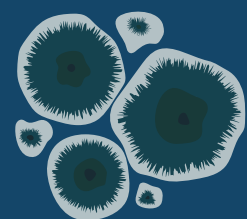


TDM Triazoles

DRUG-DRUG INTERACTIONS

Triazoles are susceptible to significant drug-drug interactions, which can greatly alter their serum concentrations and affect both efficacy and safety.

| Pharmacological Class | Interacting Drug | Effect on Voriconazole | Effect on Interacting Drug | Management | Severity |
|-----------------------|---------------------------|------------------------|----------------------------|---|--------------------|
| CYP450 Inducers | Rifampicin | ↓ Voriconazole | – | Avoid combination; use alternative antifungal | Severe (Avoid) |
| | Carbamazepine | ↓ Voriconazole | ↑ Carbamazepine | Contraindicated; monitor closely | Severe (Avoid) |
| | Phenytoin | ↓ Voriconazole | ↑ Phenytoin | Avoid or adjust dose of voriconazole and monitor levels | Moderate to Severe |
| CYP450 Inhibitors | Ritonavir (high dose) | ↓ Voriconazole | ↑ Ritonavir | Avoid combination | Severe (Avoid) |
| | Omeprazole (PPI) | ↑ Voriconazole | – | May need dose reduction of voriconazole | Moderate |
| Statins | Simvastatin, Atorvastatin | – | ↑ Statin | Avoid or choose non-CYP3A4 statin (e.g., pravastatin) | Moderate to Severe |

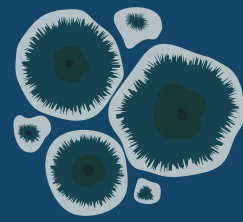


VARIABLE BIOAVAILABILITY

The bioavailability of oral triazoles can be highly variable, depending on the specific drug, formulation, and patient-specific factors (e.g., food intake, gastric pH).

Table 1 Selected examples of the pharmacokinetic interactions of anti-fungal agents

| | | Mechanism | Examples of implicated antifungals |
|------------|------|-----------|--|
| Absorption | pH | | <ul style="list-style-type: none">• Itraconazole capsules^{20–22}• Posaconazole suspension²³ |
| | Food | | <ul style="list-style-type: none">• Posaconazole suspension²³• Itraconazole (Sporanox[®])^{20,24}• Voriconazole²⁵ |

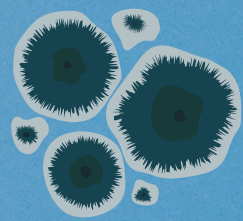


TDM Triazoles

WHY ACCURATE SAMPLING IS IMPORTANT?

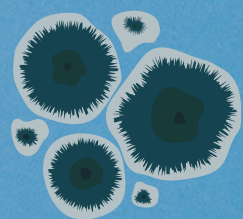
**PRE-LEVEL:
0-30MIN PRIOR TO THE NEXT
ADMINISTRATION TIME**

- In taking serum sample, the correct sampling time is crucial.
- Different sampling time represent different point in serum concentration-time curve relative to the drug dose.
- Inappropriate sampling time will lead to misinterpretation of TDM results and dosing adjustment.
- This may further put patient in risk of toxicity, treatment failure and adverse effects.



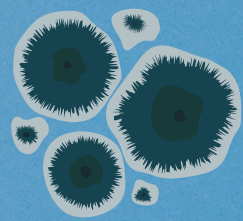
TDM Triazoles

RECOMMENDED SAMPLING TIME & REFERENCE RANGE

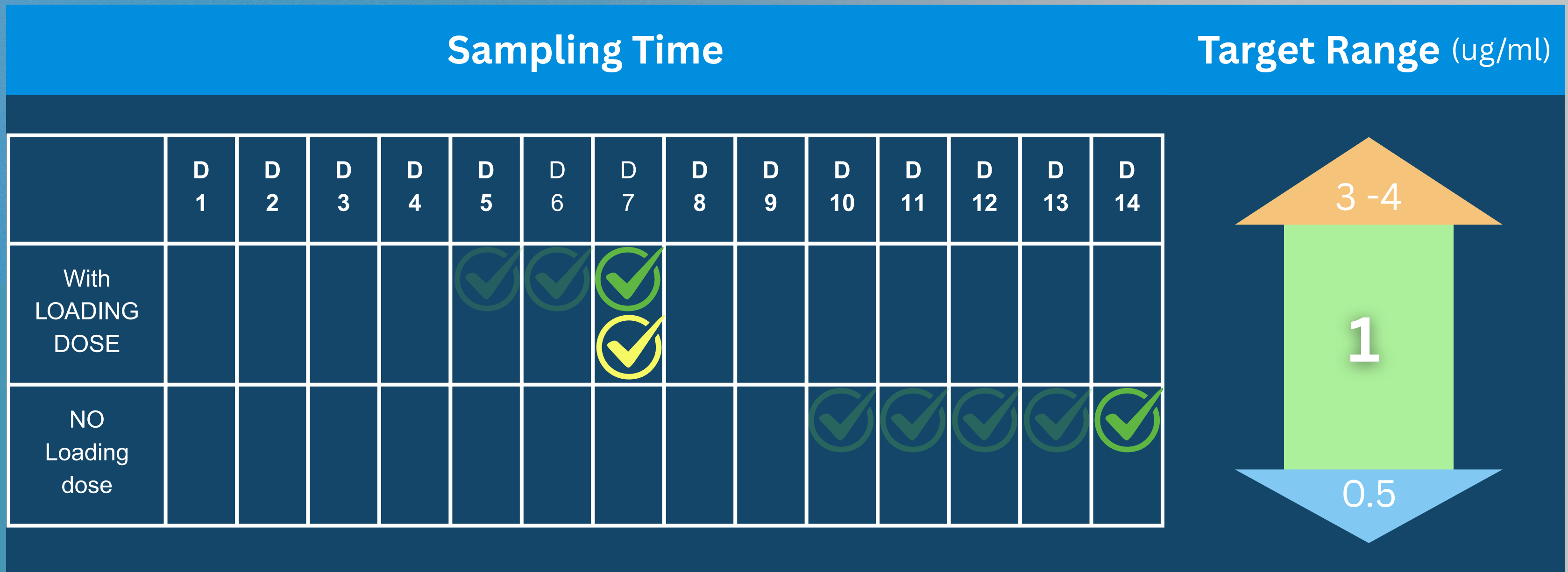


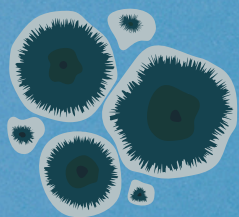
VORICONAZOLE

| | Sampling Time | | | | | | | | | | | | | | Target Range (ug/ml) |
|-------------------|---------------|-----|-----|-----|--------|-----|-----|-----|-----|------|------|------|------|------|----------------------|
| | D 1 | D 2 | D 3 | D 4 | D 5 | D 6 | D 7 | D 8 | D 9 | D 10 | D 11 | D 12 | D 13 | D 14 | |
| With LOADING DOSE | | ✓ | ✓ | ✓ | ✓ ✓ | | | | | | | | | | 4 - 5.5 1 - 2 |
| NO Loading dose | | | | | ✓ | ✓ | ✓ | ✓ | ✓ | | | | | | 0.5 |



ITRACONAZOLE



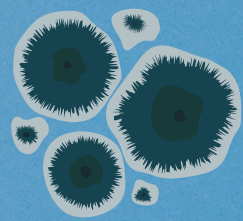


POSACONAZOLE

| | Sampling Time | | | | | | | | | | | | | | Target Range (ug/ml) |
|-------------------|---------------|-----|-----|-----|-----|-----|-----|-----|-----|------|------|------|------|------|----------------------|
| | D 1 | D 2 | D 3 | D 4 | D 5 | D 6 | D 7 | D 8 | D 9 | D 10 | D 11 | D 12 | D 13 | D 14 | |
| With LOADING DOSE | | | | | ✓ | ✓ | ✓ | | | | | | | | 3 - 3.75 |
| | | | | | | | ✓ | | | | | | | | 1 - 1.5 |
| NO Loading dose | | | | | | | ✓ | ✓ | ✓ | ✓ | ✓ | | | | 0.5 - 0.7 |

McCreary EK, Davis MR, Narayanan N, et al. Utility of triazole antifungal therapeutic drug monitoring: Insights from the Society of Infectious Diseases Pharmacists. Pharmacotherapy. 2023; 43: 1043-1050. doi:10.1002/phar.2850

Chau et al. Internal Medicine Journal (2021) 51(Suppl. 7) 37–66



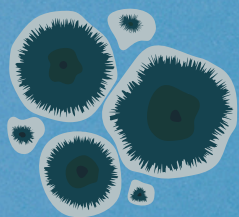
ISAVUCONAZOLE

| Sampling Time | | | | | | | | | | | | | | | Target Range (ug/ml) | |
|-------------------|-----|-----|-----|-----|-----|-----|-----|-----|-----|------|------|------|------|------|----------------------|--|
| | D 1 | D 2 | D 3 | D 4 | D 5 | D 6 | D 7 | D 8 | D 9 | D 10 | D 11 | D 12 | D 13 | D 14 | | |
| With LOADING DOSE | | | | | | ✓ | | | | | | | | | | |
| NO Loading dose | | | | | | | | | | | ✓ | ✓ | ✓ | ✓ | | |

4.6 - 5.1

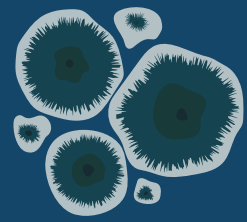
1 - 5*

0.5



FLUCYTOSINE

| Sampling Time | | | | | | | | | | | | | | Target Range (ug/ml) | | |
|--------------------------------|-----|-----|-----|-----|-----|-----|-----|-----|-----|------|------|------|------|----------------------|--|--|
| | D 1 | D 2 | D 3 | D 4 | D 5 | D 6 | D 7 | D 8 | D 9 | D 10 | D 11 | D 12 | D 13 | D 14 | <div><div></div><div>Peak level</div><div>50-75</div><div></div></div> | |
| SAMPLE POST 2 HOURS AFTER DOSE | | | | ✓ | ✓ | ✓ | ✓ | | | | | | | | | |

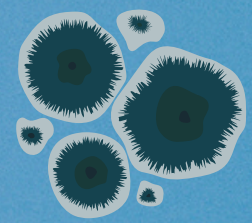


WHEN TO SAMPLE?

WITH OR WITHOUT LOADING DOSE?

- Loading dose helps to achieved steady state faster.
Thus, faster sampling time.
- In treatment, loading dose normal given to reach serum therapeutic range as soon as possible
- In prophylaxis, lower serum concentration range and no loading dose given

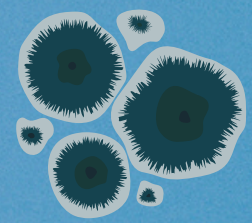




COMMON ASKED QUESTIONS

Which cohort of patients should be priorities for antifungal TDM?

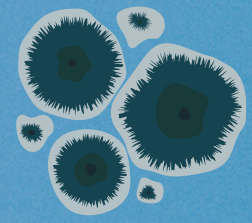
- Infection involving sanctuary sites , e.g : brain abscess, endophthalmitis
- Inadequate clinical response or breakthrough infection
- Suspected toxicity or adverse events
- Suspected genetic polymorphism
- Drug-drug interaction
- Critically ill patients
- Patients with renal and or liver failure
- Gastro-intestinal intolerance (impaired oral bioavailability)
- Extreme body weight



TDM Triazoles

COMMON ASKED QUESTIONS

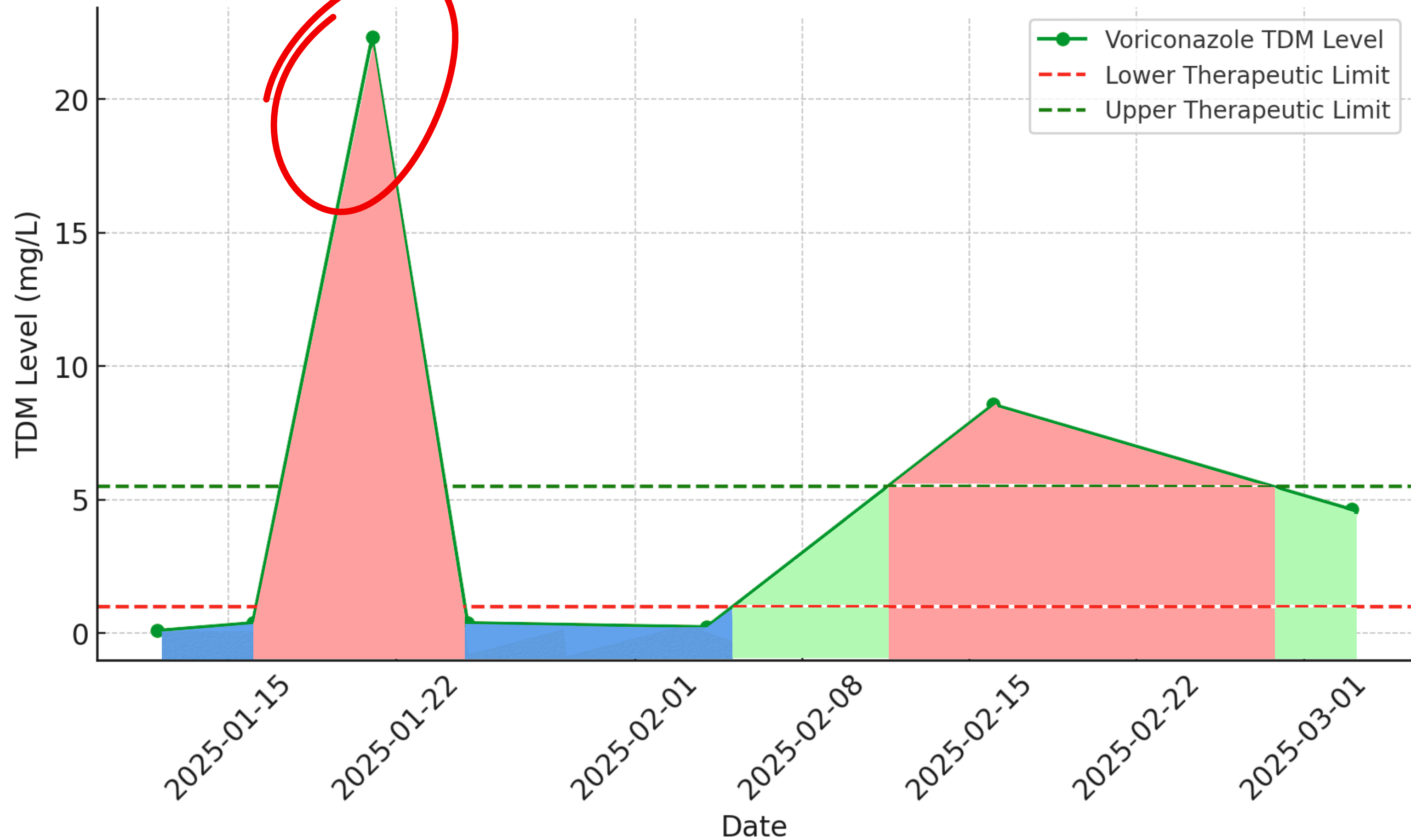
- How to process the sample after taken?
 - What are the tube to fill the blood samples in?
 - How the serum should be kept?
 - Stability of the sample to be sent/transport to outsource laboratory?
-



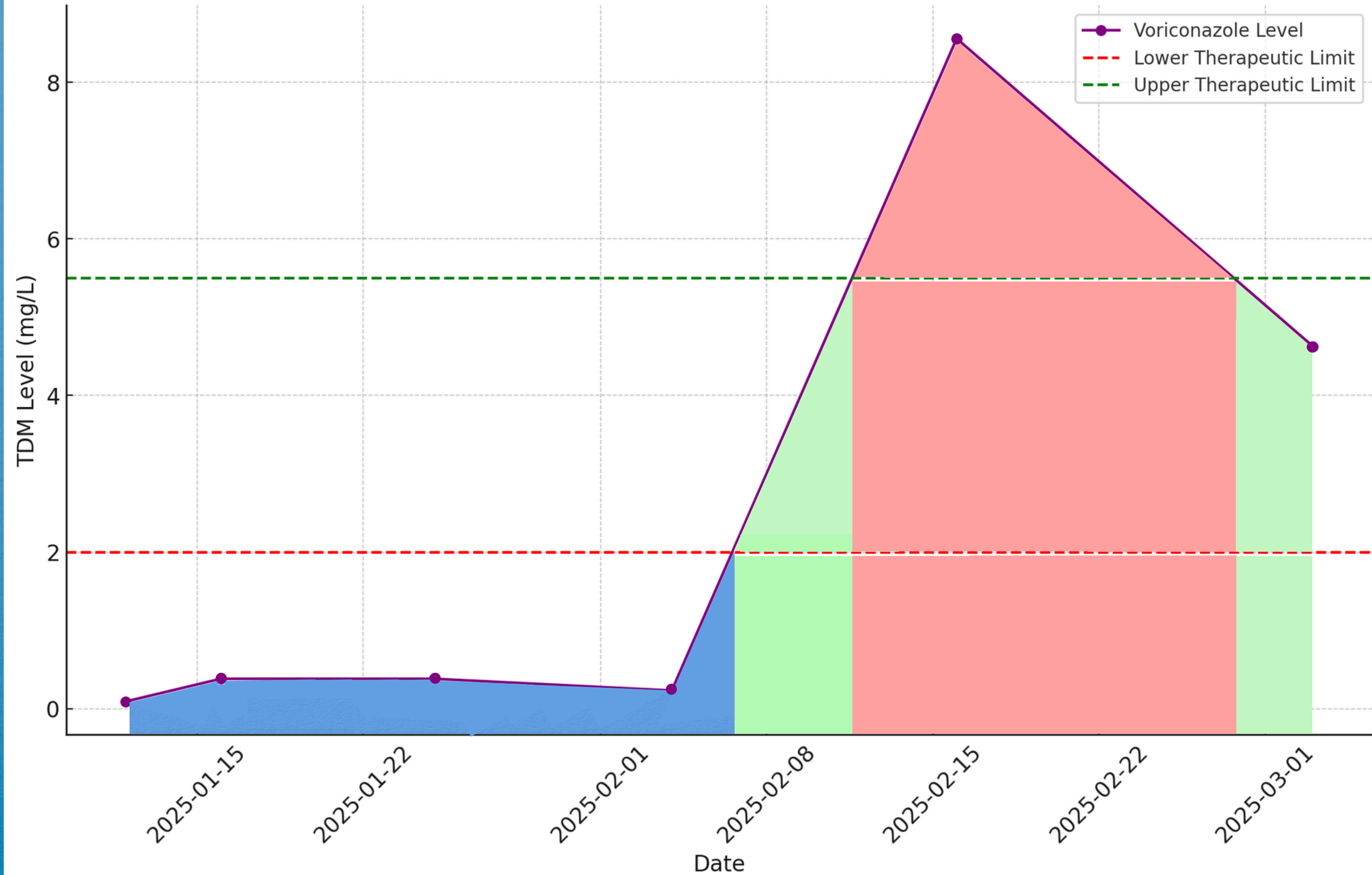
CASE SENARIO

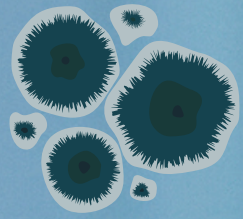
Wrong sampling time: **Post/Peak level or supratherapeutic?**

Voriconazole TDM serum levels



Voriconazole TDM Levels Over Time





TDM Triazoles

**THANK YOU FOR
YOUR ATTENTION!**

Feel free to ask questions.