NORTHWEST AIDS EDUCATION AND TRAINING CENTER

ARV Therapeutic Drug Monitoring

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Presentation prepared by:
Presenter
Last Updated: Date

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National Jewish(Denver) Req. Form

5. THERAPEUTIC DRUG MONITORING

Please provide 2 mL serum per test. The number of hours after the dose to collect "peak" concentrations is shown in parentheses after each drug name, if applicable. To test for delayed drug absorption, a second sample may be collected 4 hours after the "peak". Trough concentrations (prior to next dose) are recommended for the anti-HIV and anti-fungal drugs.

☐ABALH	Abacavir (1–2h)	☐DARU	Darunavir (2–4h)	☐LFLHL	Levofloxacin (2h)	☐RBN	Rifabutin (3h)
☐AMXLB	Amoxicillin	☐DELV	Delavirdine (2h)	☐LNZL	Linezolid (2h)	☐RIFH	Rifampin (2h)
☐AMPL	Amprenavir (2–3h)	☐EFVL	Efavirenz (5h)	☐LOPV	Lopinavir (4–6h)	☐RFPTN	Rifapentine (5h)
☐ATAZ	Atazanavir (2h)	☐EMH	Emtricitabine (1–2h)	☐MXFL	Moxifloxacin (2h)	☐RTVL	Ritonavir (2–3h)
☐AZL	Azithromycin (2–3h)	☐EMBH	Ethambutol (2–3h)	☐NLFL	Nelfinavir (2–3h)	☐SAQL	Saquinavir (2–3h)
☐CFH	Clofazamine (2–3h)	☐ETAH	Ethionamide (2h)	☐NEV	Nevirapine (2h)	☐SILLH	Sildenafil (1–2h)
☐CLART	Clarithromycin (2–3h)	☐FLUCZ	Fluconazole (2h)	☐OFLHL	Ofloxacin (2h)	☐STVLH	Stavudine (1h)
☐CMH	Capreomycin (1–2h)	☐INDL	Indinavir (1–2h)	☐PASH	P-Aminosalicylic Acid (6h)	☐SMH	Streptomycin (1–2h)
☐CIPH	Ciprofloxacin (2h)	☐INH	Isoniazid (1–2h)	☐POSA	Posaconazole (3–6h)	☐TIPV	Tipranavir (3h)
☐CORTH	Cortisol (prednisolone)	☐ITRL	Itraconazole (3–4h)	☐PZAH	Pyrazinamide (2h)	☐VDMSCB	25-OH Vitamin D_2 and D_3
☐CSH	CycloSERINE (2–3h)	☐LAMLH	Lamivudine (1h)	☐RALLH	Raltegravir (3h)	☐VORZ	Voriconazole (2h)

6. SPECIAL INSTRUCTIONS

Please list additional medications patient is currently taking here.

Sample preparation and shipment: Collect in a plain red top, 8-10 ml tube. Separate serum from cells immediately by centrifugation and aliquot into a labeled polypropylene or similar plastic tube. Use a separate tube for each test ordered. Allow room for expansion of sample inside tube. Freeze at -70°C if possible (otherwise -20°C.) Ship on ≥ 3 lbs. dry ice via overnight transport. **SHIP SAMPLES TO BE RECEIVED MONDAY THROUGH FRIDAY. DO NOT SHIP ON FRIDAY OR SATURDAY.**

INTERNAL USE

Received By | Date | Time | Condition: ☐ Frz ☐ Ref ☐ Thawed

DHHS Guidelines: TDM
Panel's Recommendations

- Therapeutic drug monitoring (TDM) for antiretroviral (ARV) agents is not recommended for routine use in the management of the HIV-infected adult **(CIII)**.
- TDM may be considered in selected clinical scenarios, as discussed in the text below.

- ***Rating of Recommendations:*** *A = Strong; B = Moderate; C = Optional*
- ***Rating of Evidence:*** *I = Data from randomized controlled trials; II = Data from well-designed nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = Expert opinion*

Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. Page H-17

DHHS Guidelines: Scenarios for Use of TDM

- Suspected Drug-Drug or Drug-Food interaction
- Pathophysiolgic states that may impair, GI, hepatic or renal fxn
- Pregnancy
- Heavily pretreated patients with VF or reduced susceptibility to ARV
- Use of alternative dosing
- Concentration dependent toxicities
- Lack of response in adherent patients

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TDM in Pediatric HIV Infection

- TDM not required, but should be considered in the following scenarios
  - Use of medications with limited PK data and therapeutic experience in children. Namely, Efavirenz in children < 3 yr old and Darunavir once daily in < 12 yr old
  - Significant Drug-Drug or Drug-Food interaction
  - Unexpected suboptimal response(good adherence, no mutations)
  - Suspected suboptimal absorption of the drug
  - Suspected dose-dependent toxicity

TDM in Pregnancy

- The DHHS Perinatal Guidelines has no consensus statement on the use of TDM in pregnancy. They recognize that the pharmacokinetics of medications may be altered during the course of pregnancy, but no general statement is given. Consult guidelines and expert opinion for each case.

Table 10a. Trough Concentrations of Antiretroviral Drugs for Patients Who Have Drug-Susceptible Virus

Drug	Concentration (ng/mL)
Suggested minimum target trough concentrations in patients with HIV-1 susceptible to the ARV drugs2-	
Fosamprenavir	400(measured as amprenavir)
Atazanavir	150
Indinavir	100
Lopinavir	1000
Nelfinavir	800
Saquinavir	100-250
Efavirenz	1000
Nevirapine	3000

Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. p H-19

Table 10b. Trough Concentrations of Antiretroviral Drugs for Treatment-Experienced Patients with Virologic Failure

Drug	Concentration (ng/mL)
Suggested minimum target trough concentrations for ART-experienced patients who have resistant HIV-1 strains	
Maraviroc	>50
Tipranavir	20 500
Median (Range) Trough Concentrations from Clinical Trials	
Darunavir (600 mg BID w/Rit)	3300 (1255 – 7368)
Etravirine	275 (81 – 2980)
Raltegravir	72 (29 – 118)

Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. p H-19

DHHS Guidelines: Factors That Limit Use of TDM

- Lack of large studies showing clinical/virologic benefit
- Lack of established therapeutic ranges for all ARV
- INTRApatient variability
- Lack of availability of labs with proper QA/QC
- Lack of expertise to interpret and act on results

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DHHS Guidelines: ARV Classes and TDM

- **PI, Non-NRTI, Integrase Inhib:** Potential for TDM exists. However, there are limited data for relationships between concentration-response and concentration-toxicity . Consult latest PK info for a particular drug if TDM used.
- **CCR5 Antagonists:** Trough concentration shown to be important in experienced patients. Limited experience
- **NRTIs:** Relationships between plasma concentrations of NRTIs and their intracellular(active) forms have not been established. Use is essentially confined to research and PK drug interaction studies.

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TDM : Case (2006)

- 25 yo male with hx of new onset TC seizures treated with phenytoin at a regional hospital. After another seizure while on phenytoin, he was admitted to HMC where dx of HIV and toxo made.
  - Treated for toxo (sulfadiazine, pyrimethamine, leucovorin)
  - Continued on phenytoin
  - HAART Truvada/atazanavir/ritonavir

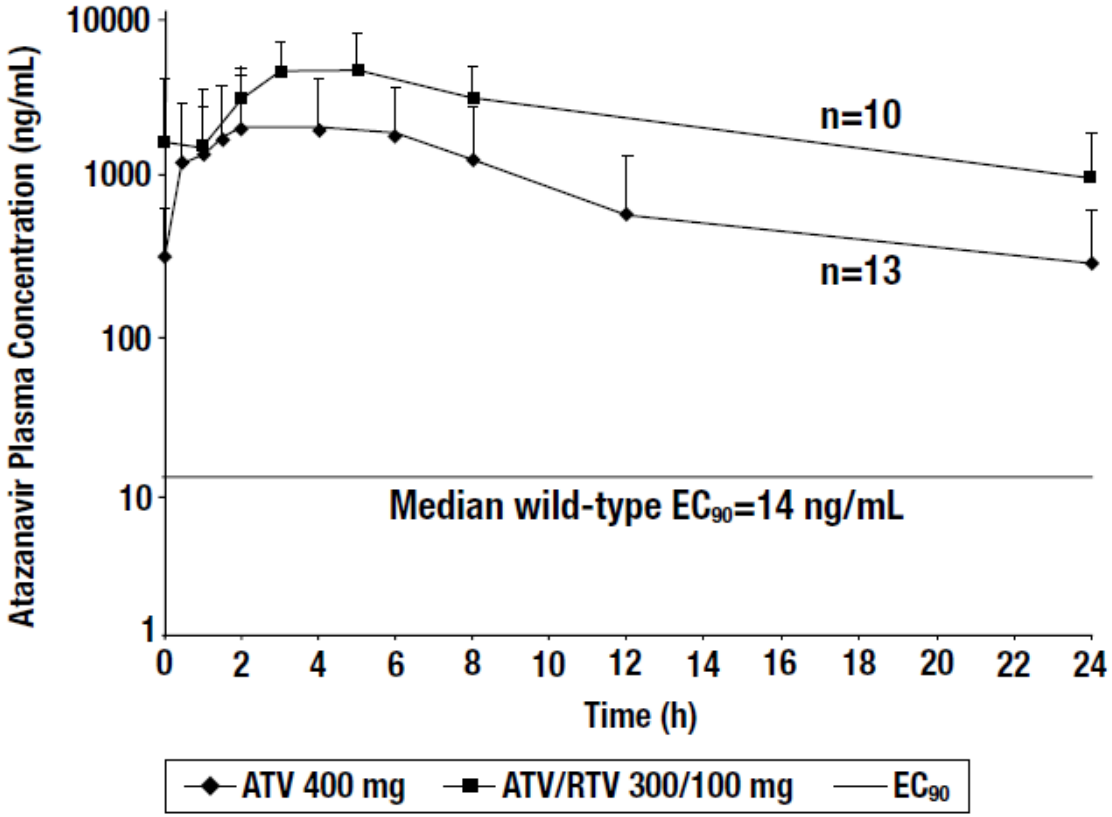
TDM Case (2006)

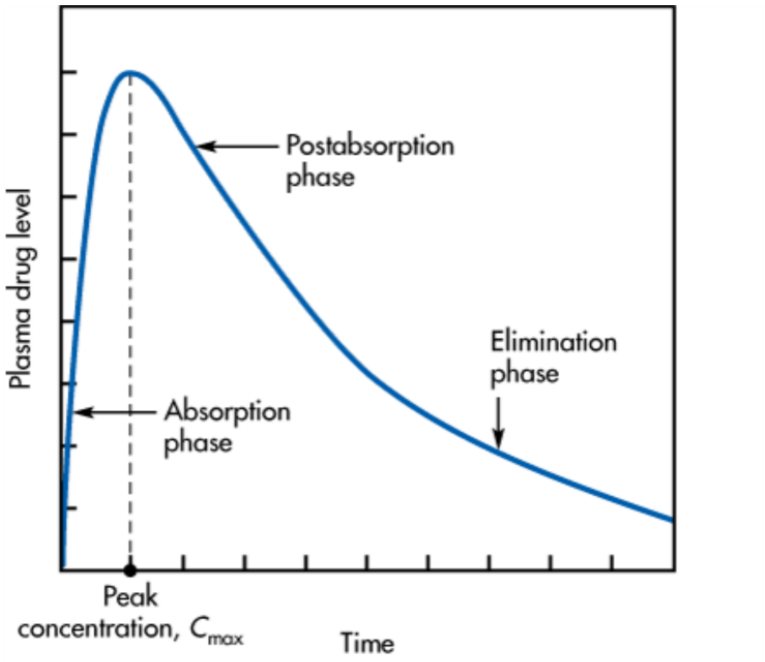
Date	Atazanavir Level mcg/mL*	Dose (ATZ/rit)	VL
4/12			413 000
5/15 (approx)		start TDF/ATZ/rit	
6/12	0.05	300/100	52 800
7/7	0.61	300/100 BID	1 210
7/17	0.46	300/100 BID	
8/3			294

*Per National Jewish at the time: trough should be greater than 0.15 mcg/mL in treatment naive

Atazanavir PK (from Package Insert)

Figure 1: Mean (SD) Steady-State Plasma Concentrations of Atazanavir 400 mg (n=13) and 300 mg with Ritonavir (n=10) for HIV-Infected Adult Patients



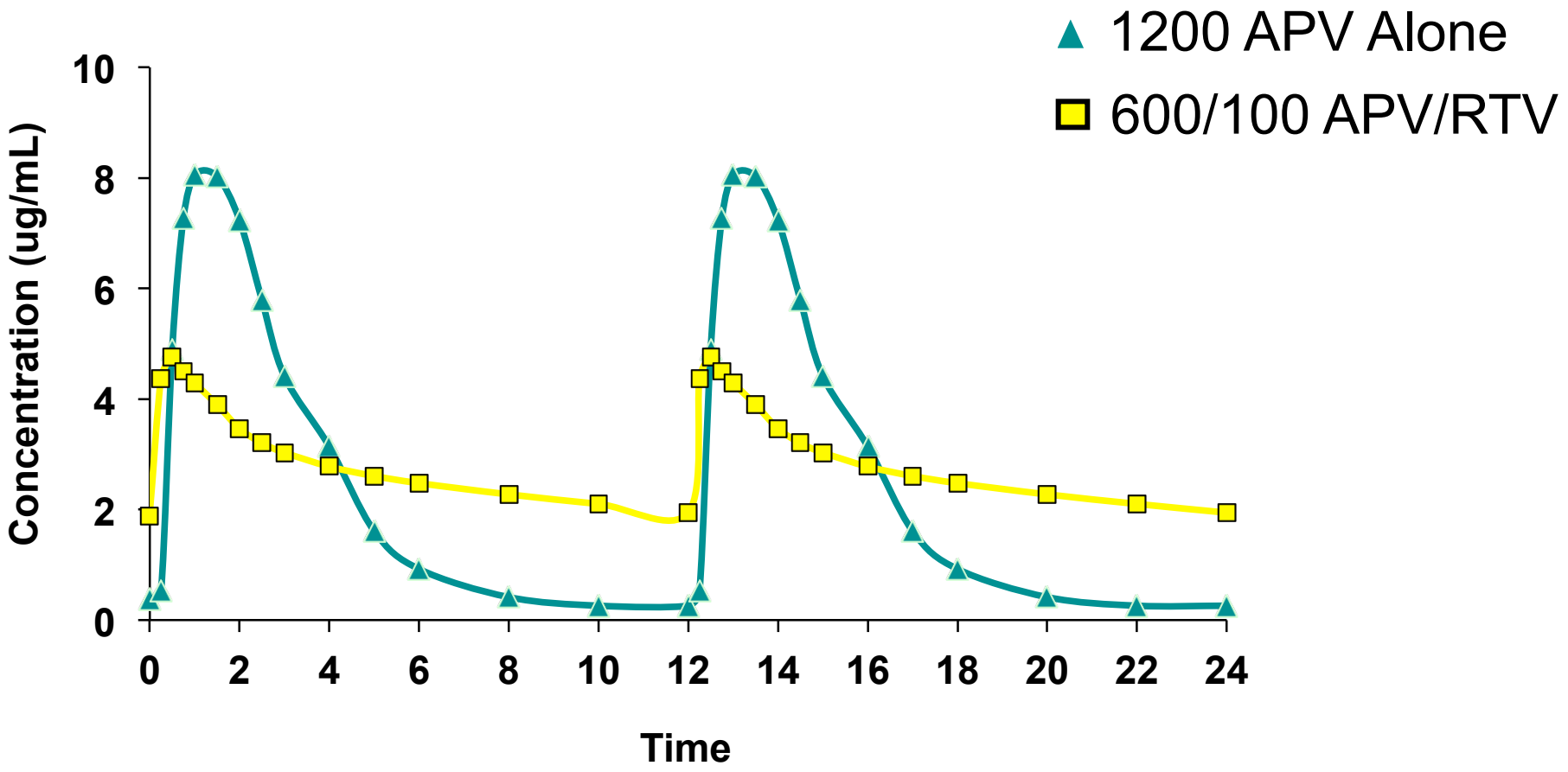


Source: Shargel L, Wu-Pong S, Yu ABC: *Applied Biopharmaceutics & Pharmacokinetics, 6th Edition*: www.accesspharmacy.com

Legend:

Plasma level–time curve for a drug given in a single oral dose. The drug absorption and elimination phases of the curve are shown.

Comparative Pharmacokinetics of Amprenavir Boosted by Ritonavir versus Standard Dose Amprenavir



Using TDM Kinetics Practical Issues

- Trough may not be easily obtained due to patient dosing time
- May need to estimate trough if not drawn on time. Use PK curve and half-life to estimate(with caution)
- Drawing a “random” level too close to peak
- Shipping restrictions/samples not accepted over the weekend. Turn around time 1-2 weeks.
- Not confirming dose and time of last dose
- Observationally induced adherence
- Lack of data on dose adjustments

TDM Practical Issues: Random vs Timed

- Random
  - Easier to get
  - Less useful for dose adjustment
  - Useful to confirm adherence or get a rough idea that drug in being absorbed

- Timed
  - If evaluating a significant drug interaction, this would be preferred
  - Can be difficult to get
    - Patient instructions
    - Staff executing and documenting correctly