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Pharmacological determinants of long-term treatment success

DuPont Pharma

Pharmacological Issues with Antiretroviral Therapy

- Intrinsic potency
- Bioavailability
- Effect of food and other drugs on absorption
- Protein binding
- Plasma half-life
- Intracellular half-life
- Intracellular activation
- Sanctuary sites
- Drug interactions
  - unfavourable
  - pharmacoenhancement
- Tolerability and toxicity
- Dosage regimens in special patient groups

Three Key Parameters

- Potency of drug against the virus
- Protein binding
  – must have adequate concentration
  in vivo of free drug
- ***In vivo*** pharmacokinetics
  (C_{max}, C_{min}, AUC, half-life)

Activation of Nucleoside Analogues

Adenosine Thymidine

ZDV

ABC

Adenosine Phosphotransferase

ZDV-MP

3TC-MP

Cytosolic Enzyme

ZDV-DP

3TC-DP

Kinase

Kinase

ZDV-TP

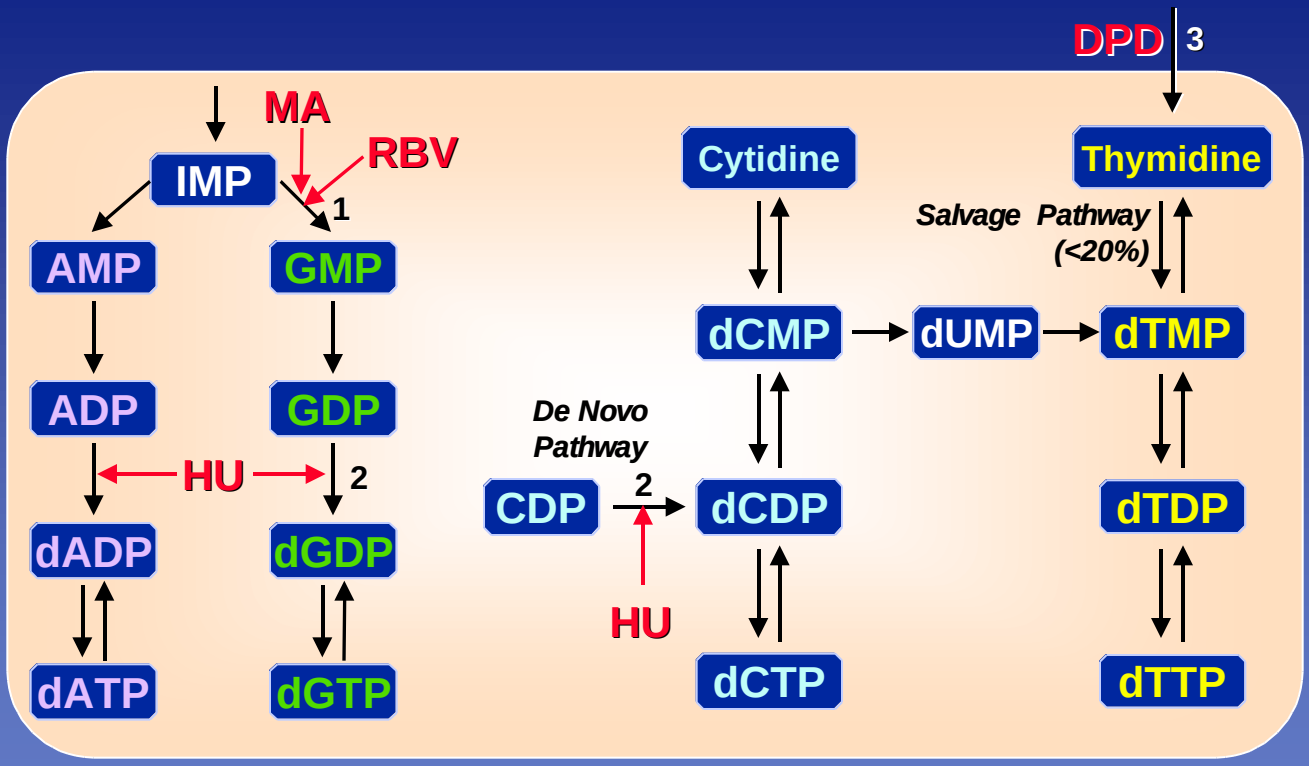
ddC-TP

3TC-TP

ddA-TP

CBV-TP

Metabolic Pathways of Cellular Nucleosides



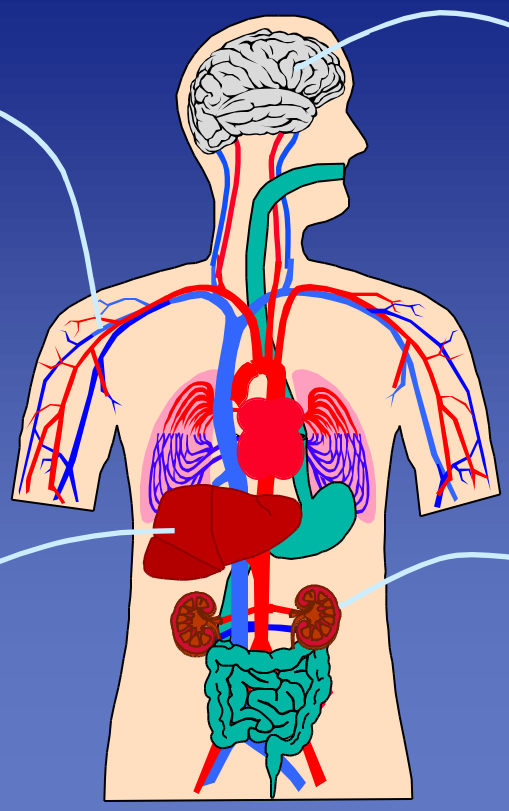
1. IMP dehydrogenase
2. Ribonucleotide reductase
3. Carrier-mediated transport

MRP4: A previously unidentified factor in resistance to nucleoside-based antiviral drugs

"Because MRP is expressed in normal tissues and because HIV can infect a variety of cell types, high levels of MRP4 expression at some anatomical sites may allow growth and evolution of drug-resistant HIV by decreasing the amount of intracellular drug to levels below that necessary to inhibit HIV replication."

Schuetz et al.
Nature Medicine, September 1999

Organ Distribution of Transport Proteins



Brain

MDR1 OAT3
MRP1 OATP1
MRP5 OATP2

Lymphocytes

MDR1
MRP4

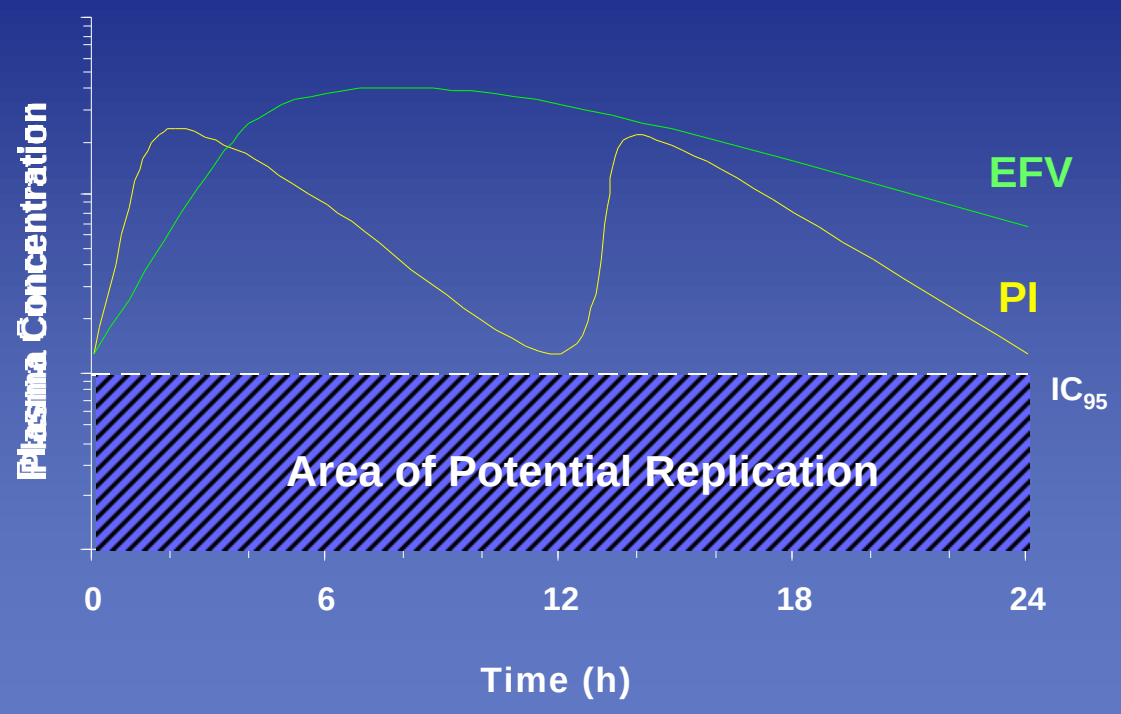
Liver

LST1 OAT2
MDR1 OAT3
MRP2 OATP1
MRP3 OCT1
NTCP1 SPGP

Kidney

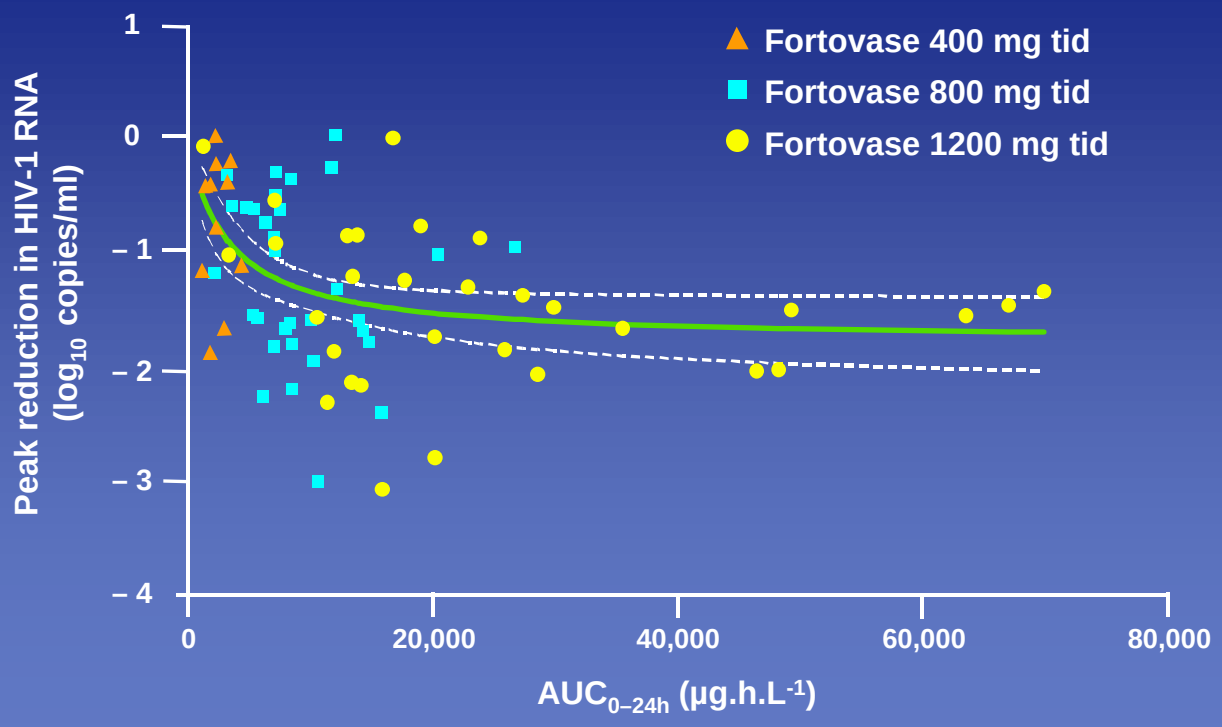
MDR1 OATP1
MRP1 OATP2
NTCP1 OCT1
OAT1 OCT2
OAT3

Pharmacokinetic profile of a single PI administered twice daily and efavirenz given once daily

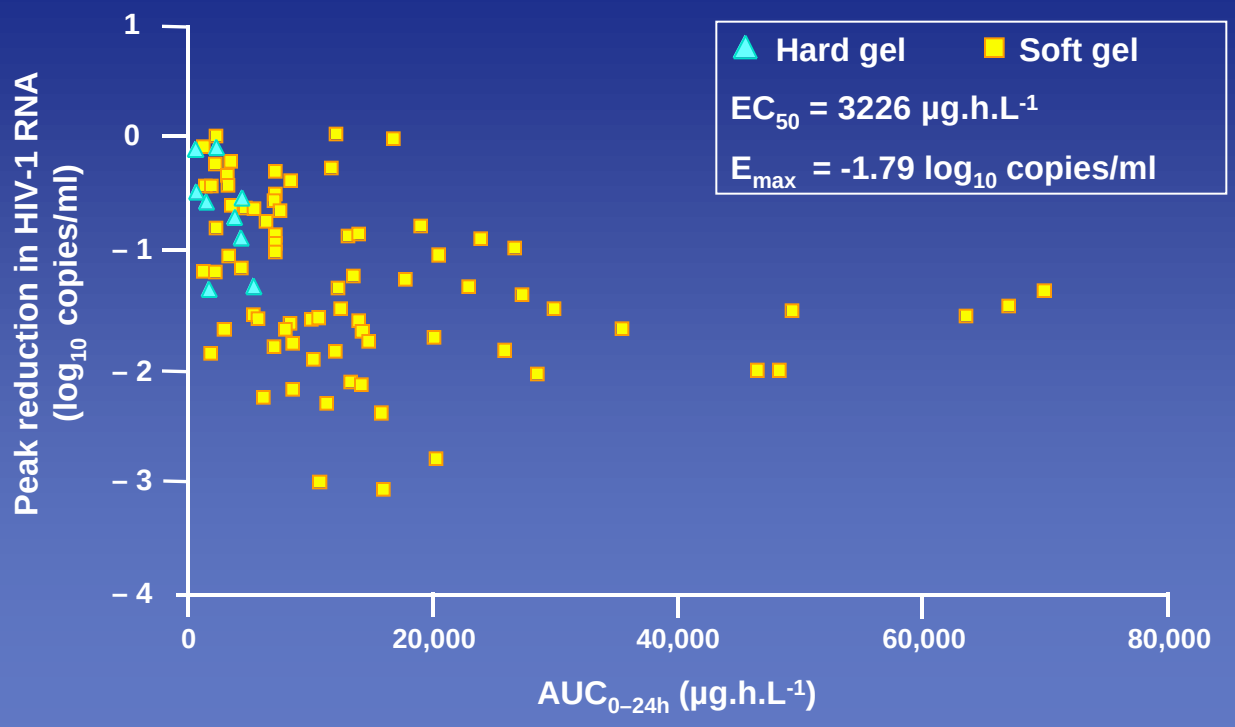


NV 15107 Study

Selection of Doses



Relationship between peak reduction in plasma HIV RNA and SQV $AUC_{0\text{-}24h}$ for hard and soft gel formulations



Gieschke et al., 1999

Target Concentration

- Exposure target of approximately 20,000 µg.h.L^{-1} with maximal virological response.
- Target exposure may differ depending on concomitant therapy and patient population.
- Exposure-response modelling gave the optimal dose of SQV sgc of 1200 mg tid.

VIRADAPT

Design

- Retrospective analysis
- 81 subjects; all received PI in salvage regimen
- At least 3 samples available for analysis

Results

- Negative correlation between drug concentration and VL
- Patients subdivided:

Optimal Concentration	Suboptimal Concentration
$C_{trough} > IC_{50}$ on 2 or more occasions	$C_{trough} < IC_{50}$ on 2 or more occasions
↓	↓
-1.23 log at 48 weeks	-0.24 log at 48 weeks

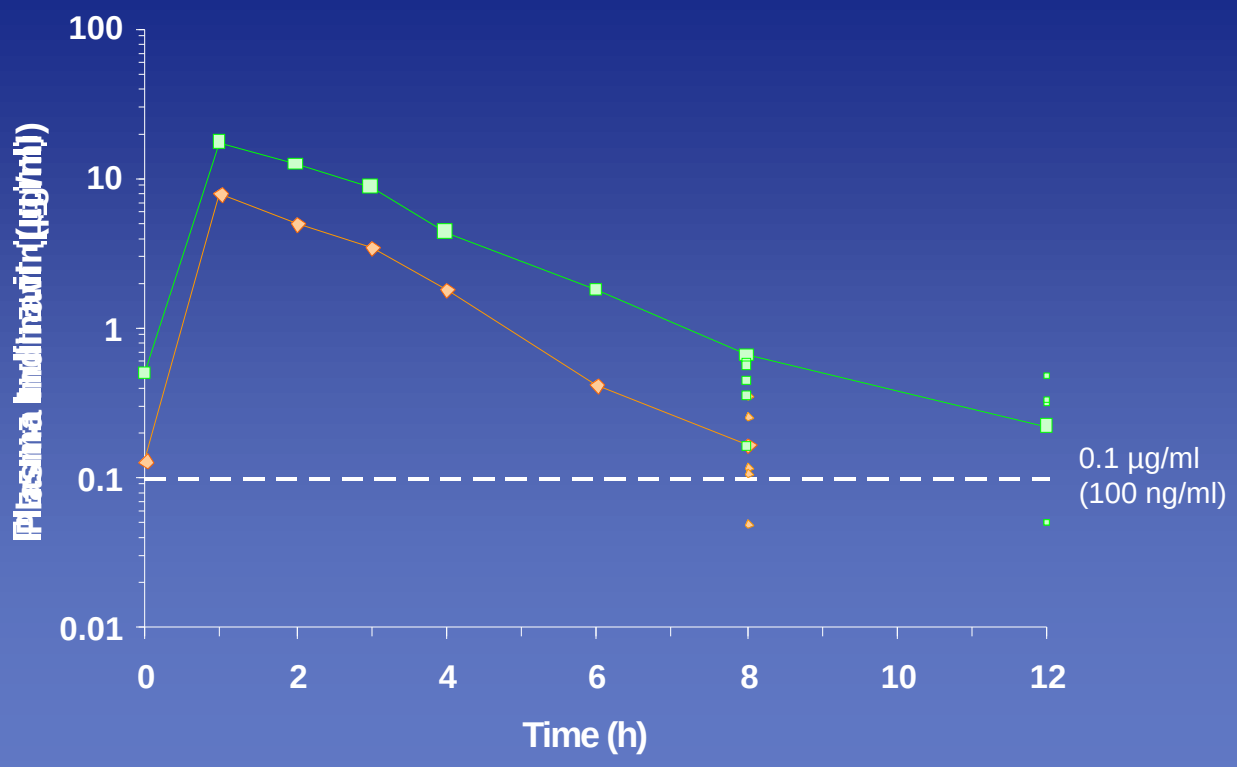
Arguments for TDM of PIs

- Low plasma concentrations correlate with clinical failure
- Marked inter-individual variability in plasma drug concentrations
- Complex drug interactions
- High plasma concentrations may correlate with toxicity
- PI disposition affected by liver dysfunction
- Assessment of poor adherence in selected patients
- Cost of therapy

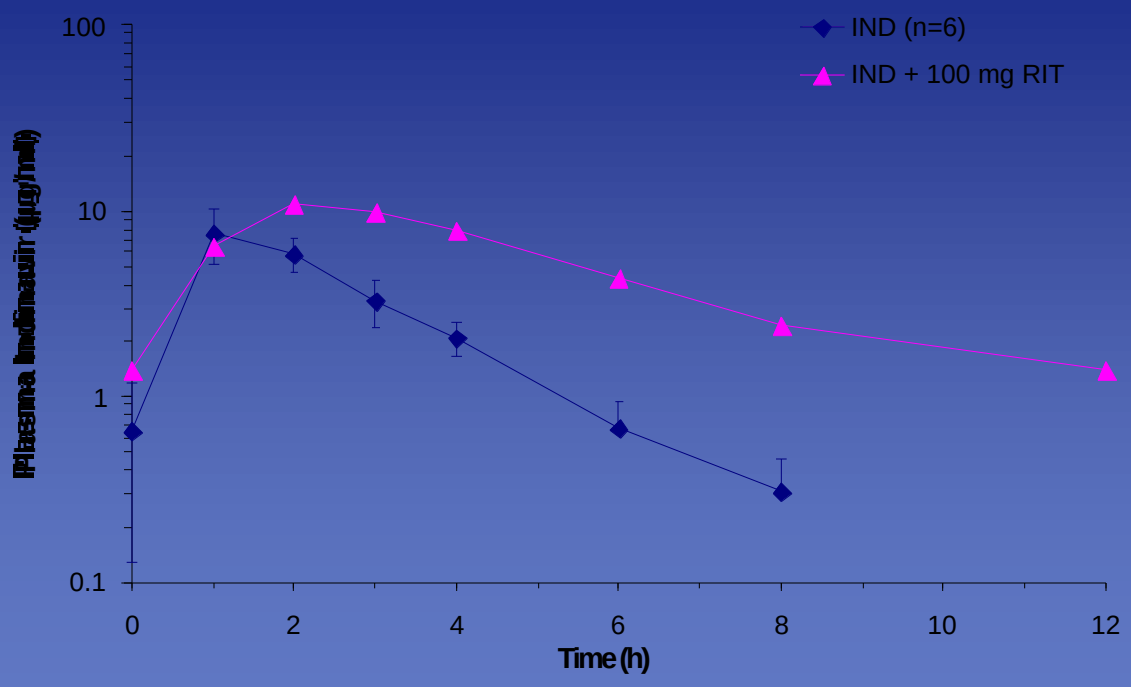
Potential Problems with TDM

- Relatively small data sets giving concentration-response relationships
- Target PI concentrations largely defined from ***in vitro*** studies with exposure to single PI
  ? Antiretrovirals in combination
- Changing patterns of adherence
- What measure is best ?
  - AUC
  - Trough
  - Trough and peak

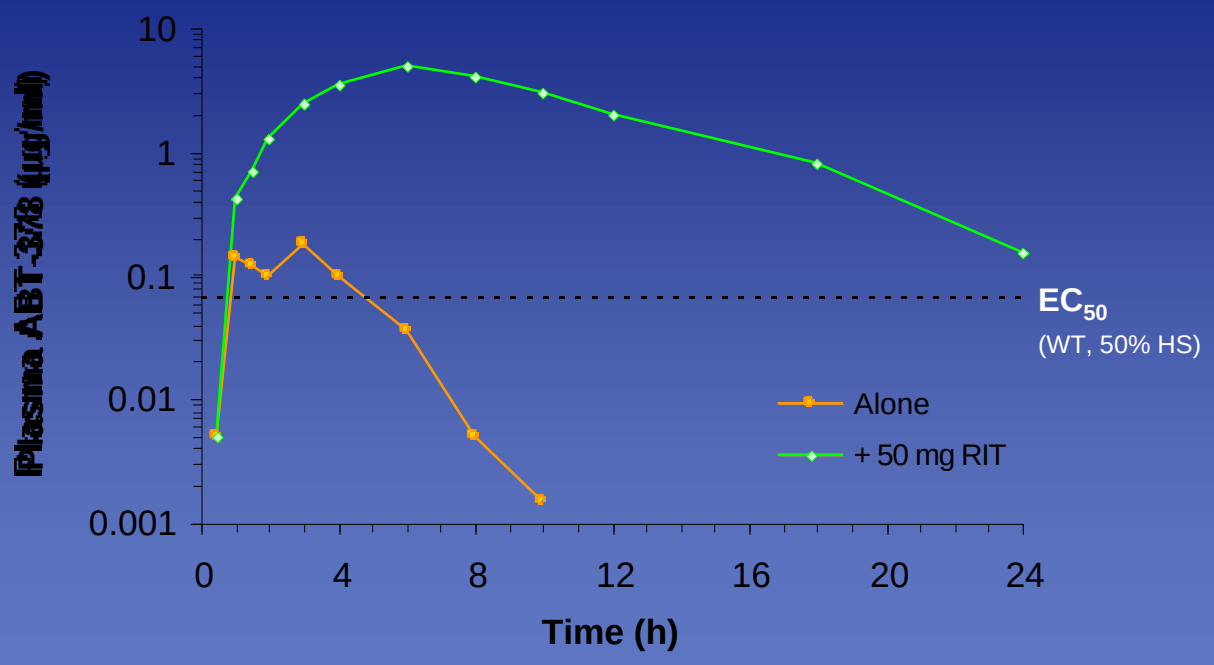
Indinavir tds *vs* bd dosing



Effect of ritonavir (100 mg) on indinavir pharmacokinetics



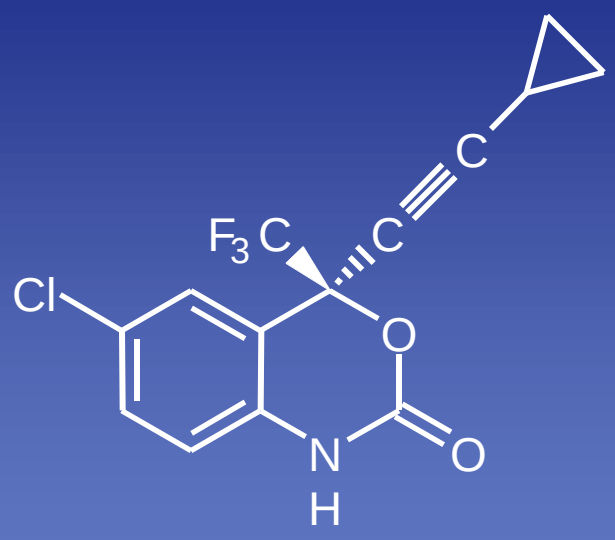
ABT-378



Sham *et al.*, 1998

Efavirenz

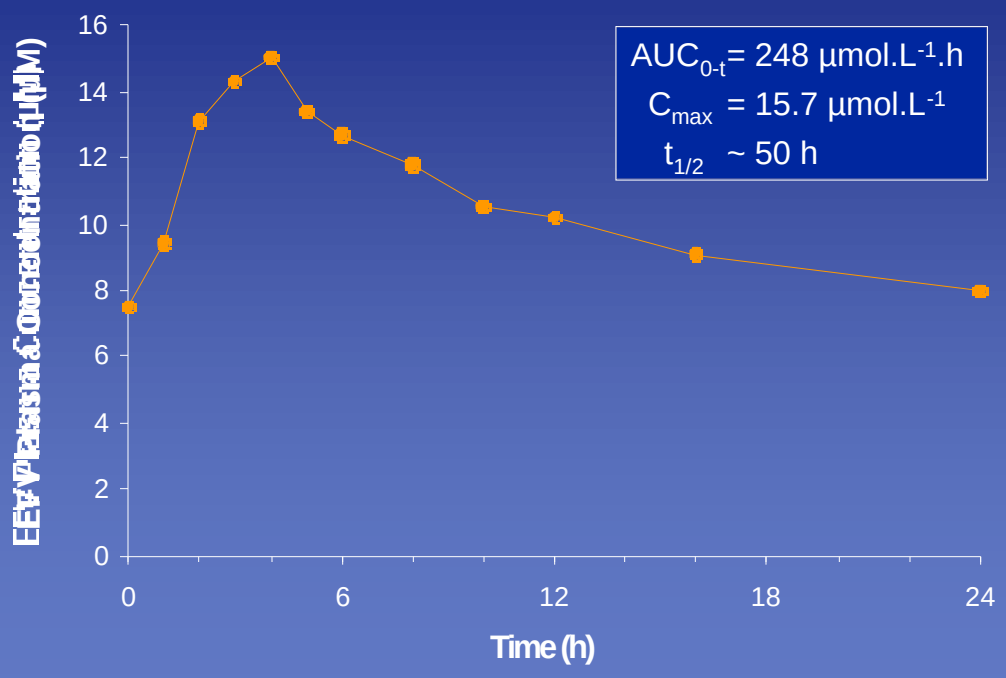
(SUSTIVA™, STOCRIN™)



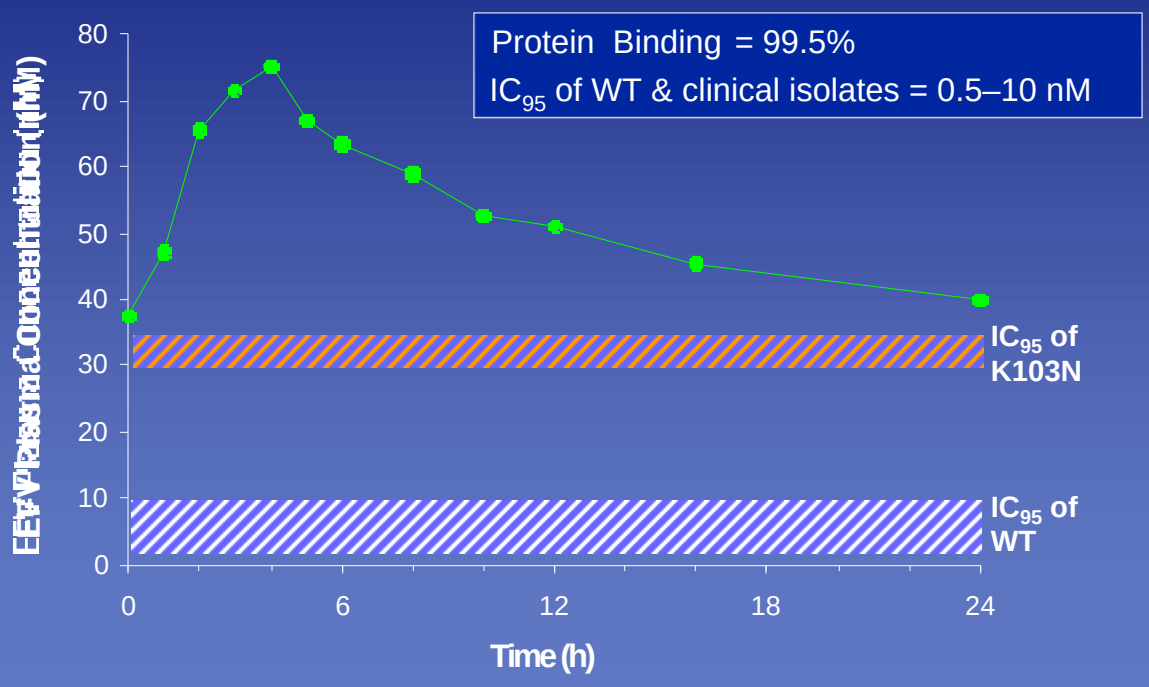
Efavirenz – Summary of Pharmacokinetics

- Good oral absorption; can be given without regard to food
- Half-life 40–55 h; allows once daily dosing
- Highly protein bound (99.5%), but penetrates CSF
- Metabolised by CYP3A4 (also CYP2B6)
- Induces CYP3A4 (also autoinduction)
- Inhibits CYP3A4
- Renal excretion as glucuronide conjugate

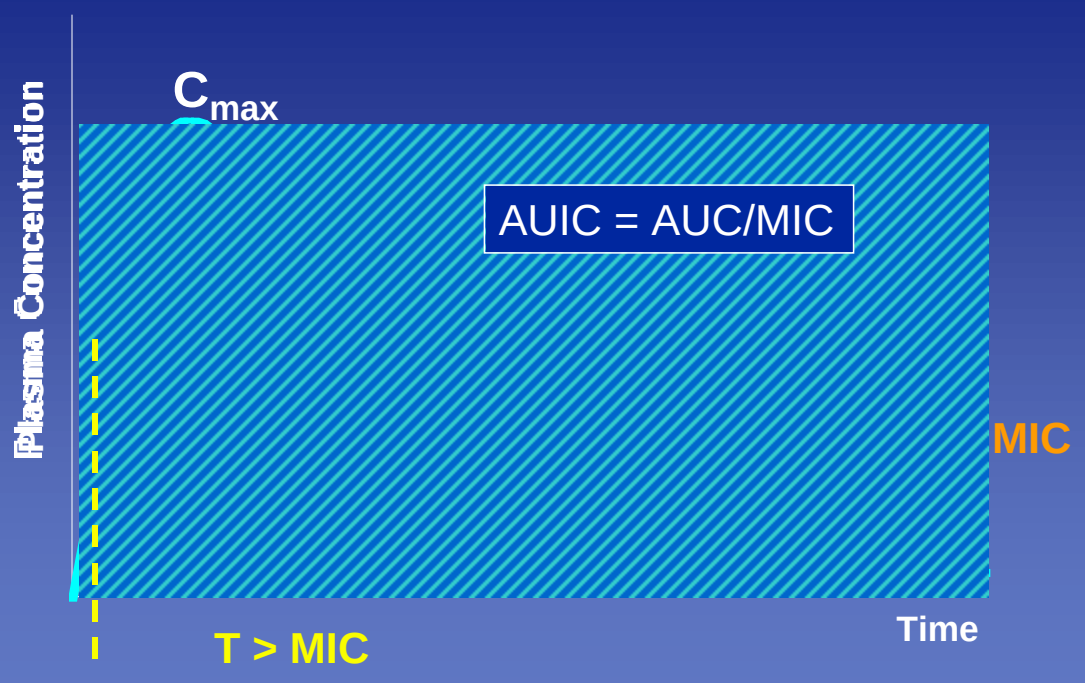
Efavirenz Mean Plasma Concentration



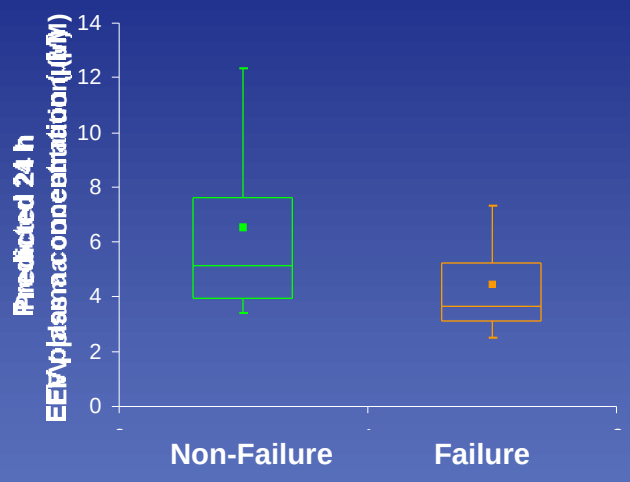
Efavirenz “Free” Plasma Concentration

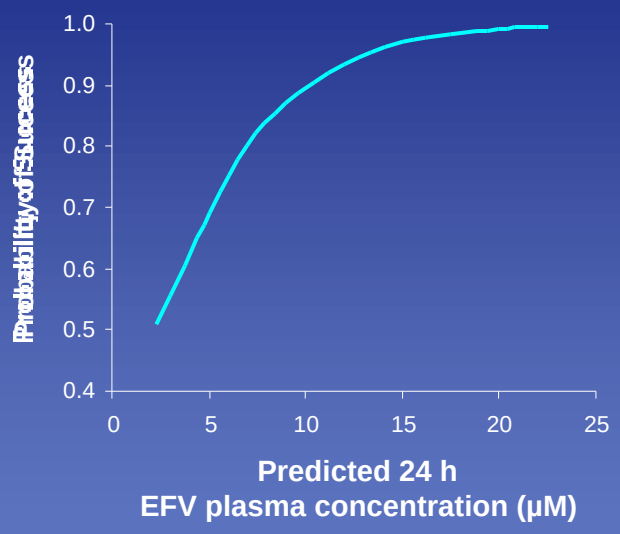


Pharmacokinetic-Surrogate Relationship



Population Pharmacokinetics of Efavirenz





Efavirenz – Induction & Inhibition

CYP3A4
INDUCED

SQV

EFV

SQV

EFV