

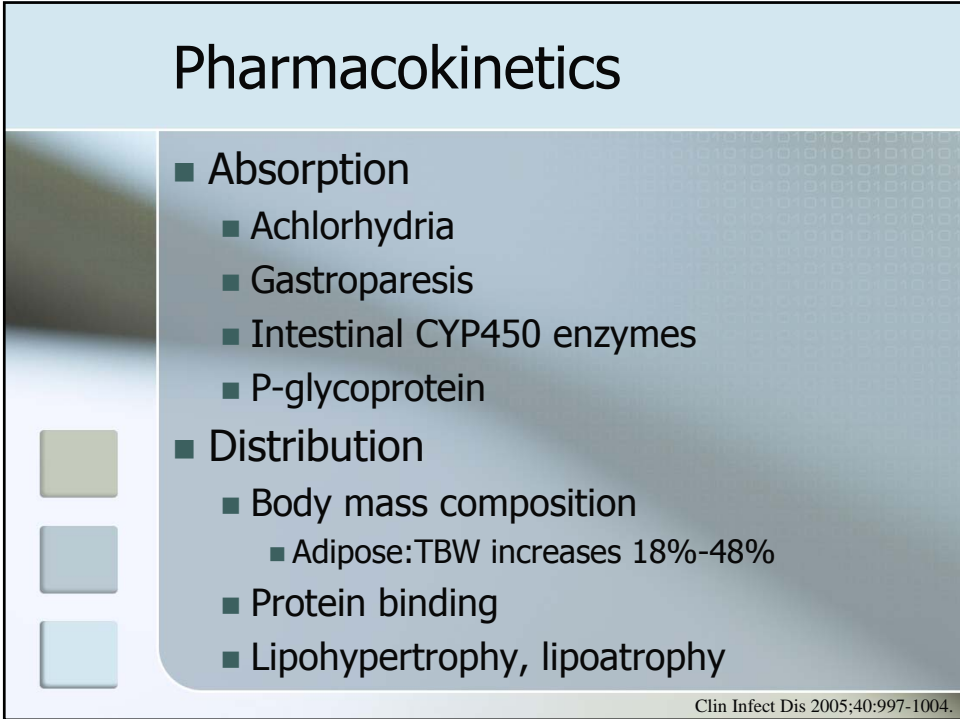


Dosing and Interactions

Pharmacokinetics and Pharmacodynamics

John Williamson, PharmD

Pharmacokinetics

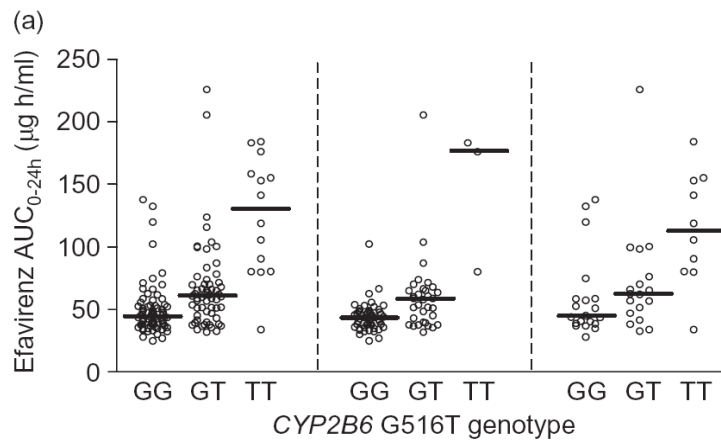
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- Absorption
 - Achlorhydria
 - Gastroparesis
 - Intestinal CYP450 enzymes
 - P-glycoprotein
 - Distribution
 - Body mass composition
 - Adipose:TBW increases 18%-48%
 - Protein binding
 - Lipohypertrophy, lipoatrophy

Clin Infect Dis 2005;40:997-1004.

Metabolism

- Age-related hepatic dysfunction
 - 0.5-1.5% decrease in hepatic blood flow per year after age 25
 - Liver mass decreases with age
 - Phase 1 enzymes (e.g. CYP450)
 - Phase 2 enzymes (e.g. conjugation)
- Co-infection with HCV
- CYP450 enzyme polymorphisms
 - Efavirenz and CYP2B6

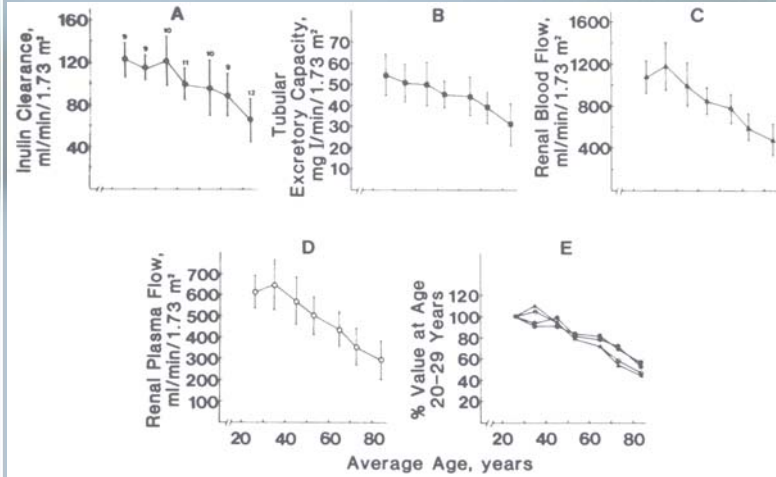
Efavirenz AUC by genotype



- Genotype associated with CNS adverse effects at week 1
- Median age = 38

AIDS 2004;18:2391-2400.

Renal Function



J Clin Invest 1950;29:496-507.

Tenofovir Expanded Access

France, Germany, Italy

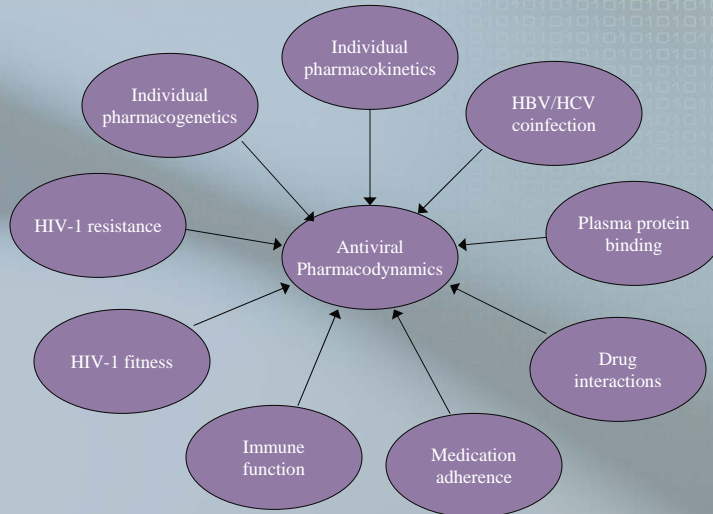
Serum creatinine grade	Baseline (n=2790)	On study (n=1704)
Grade 1 (≥ 0.5 mg/dL increase)	N/A	26 (1.5)
Grade 2 (2.0-3.0 mg/dL)	2 (0.1)	6 (0.4)
Grade 3 (3.1-6.0 mg/dL)	0	4 (0.2)
Grade 4 (≥ 6.0 mg/dL)	1 (<0.1)	1 (0.1)

	OR (95% CI)	P value
Grade 1 or more		
Age	1.05 (1.01-1.09)	0.021
Other nephrotoxic medication	2.4 (1.08-5.34)	0.032
Grade 2 or more		
Baseline creatinine	17.4 (1.64-184.1)	0.018

Median age 42

AIDS 2007;21:1273-81.

Pharmacodynamics



Adapted from Lancet Infect Dis 2006;6:215-25.

Inhibitory Quotient

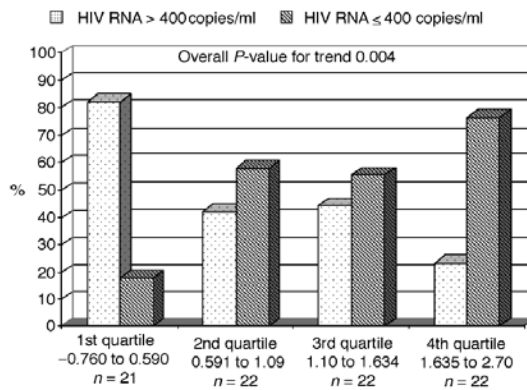


Fig. 1. Bar chart of percentage of individuals with detectable (> 400 copies/ml) versus undetectable (≤ 400 copies/ml) HIV-RNA viral load at week 48 and inter-quartile 80% clinical cut-off normalized IQ (CCO-NIQ) by intent-to-treat.

AIDS 2005;19:1393-99.

Research Opportunities

- Effects of altered PK
 - Dosing
 - Toxicity
- Pharmacogenetics
- Impact of immune senescence on pharmacodynamics
- Changing paradigm of HAART
 - CCR5 antagonists
 - Integrase inhibitors