Pharmacometric Approaches to Adherence Assessment

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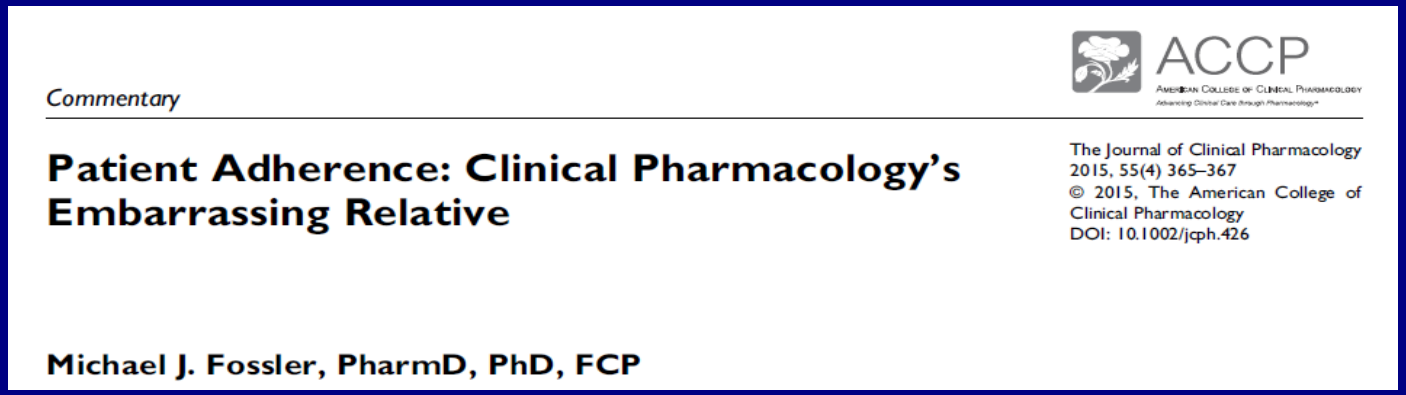
Introduction

- What if there was a covariate which
  - Can be reliably measured/estimated?
  - Can reduce residual variability in PPK parameters by as much as ***50%?***
  - Is highly predictive of clinical efficacy?

Would you push for its inclusion in clinical trials?
Would you include its effect in your simulation work?

That Covariate is Adherence….



Commentary

Patient Adherence: Clinical Pharmacology's Embarrassing Relative

The Journal of Clinical Pharmacology
2015, 55(4) 365–367

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- Despite the obvious connection between taking a medication as directed and its effect, adherence is almost never
  - Measured in clinical trials
  - Pre-specified in the analysis plan and used in the analysis
  - ***Investigated for its effect on end-points via simulation***

Why You should Care about Adherence

Failure to account for adherence may make an effective drug look ineffective

- 8 week trial of weight-loss agent
- Adherence determined by plasma concentrations
- Those who were adherent lost weight – those who were not *gained* weight
- Combined analysis without adherence would likely show little/no effect (weighted average = -0.7)

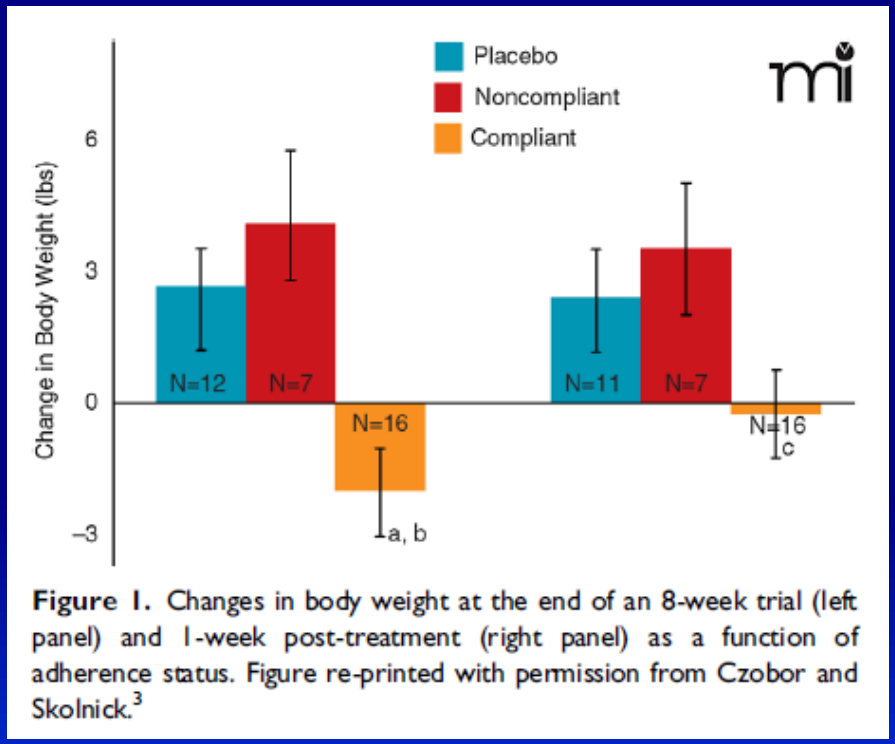


Figure 1. Changes in body weight at the end of an 8-week trial (left panel) and 1-week post-treatment (right panel) as a function of adherence status. Figure re-printed with permission from Czobor and Skolnick.[3]

Why You should Care about Adherence

Failure to account for adherence may make PPK modeling of patient data impossible

- Vrijens et al. , modeled lopinavir PK data from 35 HIV+ patients
- Using “steady state” assumption, model would not even converge
- In contrast, using electronically-captured dosing data, model converged and fit the data well

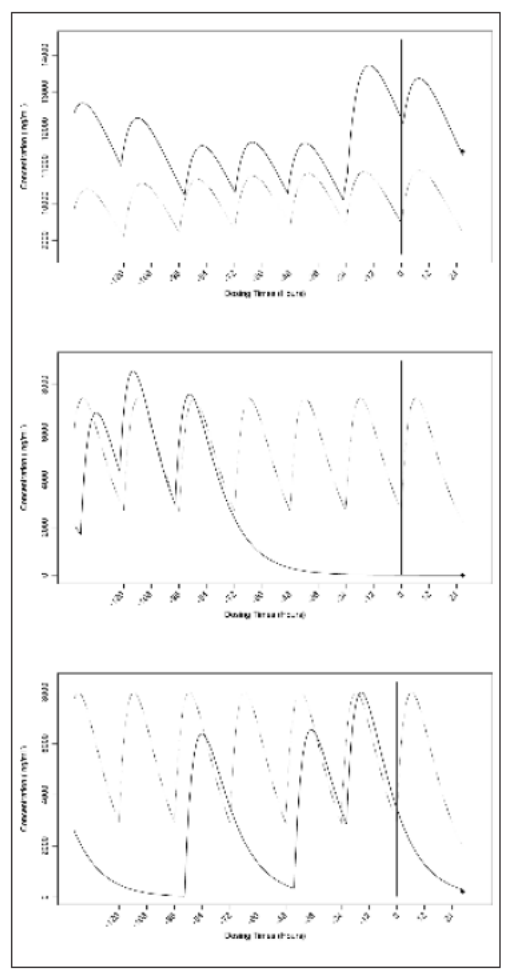


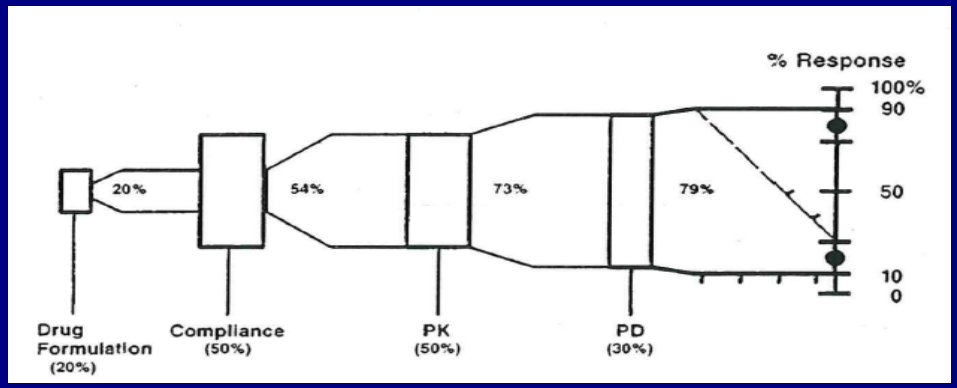
Figure 4. Individual qd patient concentration profile plots.

JCP (2005) 45:461-67

Why You should Care about Adherence

Failure to account for covariates which have large effects (like adherence) may mask the effects of other covariates

- Harter and Peck (1991) - Total variability is the cumulative sum of the square root of the sum of squares of all factors affecting response
- If you reduce the variability due to formulation (20%) to zero, the total variability will go from 79% to 77%
- Reduce adherence variability (50%) to zero brings the total ***down to 62%***
- Worrying about small sources of variability without accounting for large sources is not productive

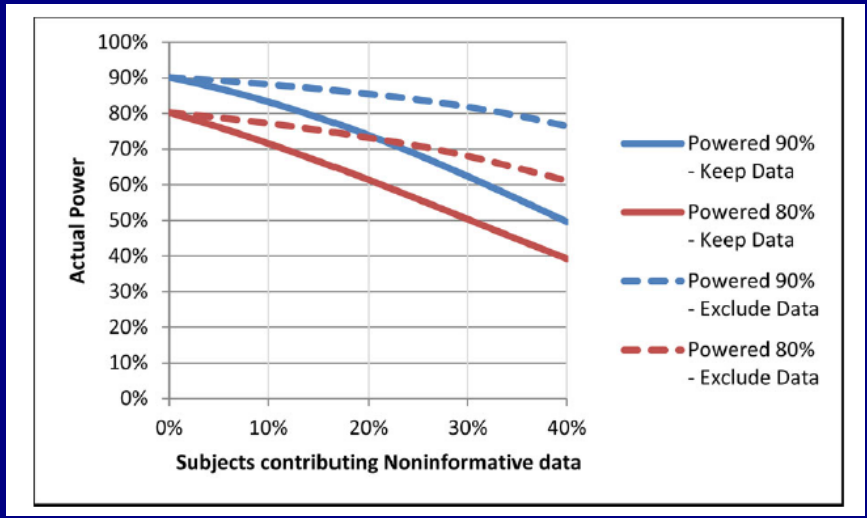


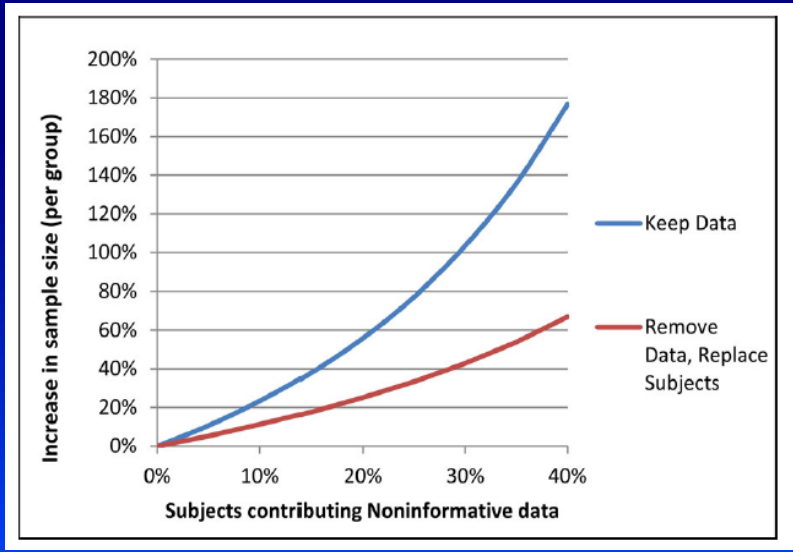
$$\sigma^2_{total} = \sqrt{(\sigma_1^2 + \sigma_2^2 + \sigma_3^2 + \sigma_4^2 \ldots\ldots}$$

ANYAS (1991)

Failure to account for adherence can have a profound effect on study power

- A study powered at 90% with 30% non-adherent patients will actually only have ~60% power
- Sample size would have to double to overcome the non-informative data

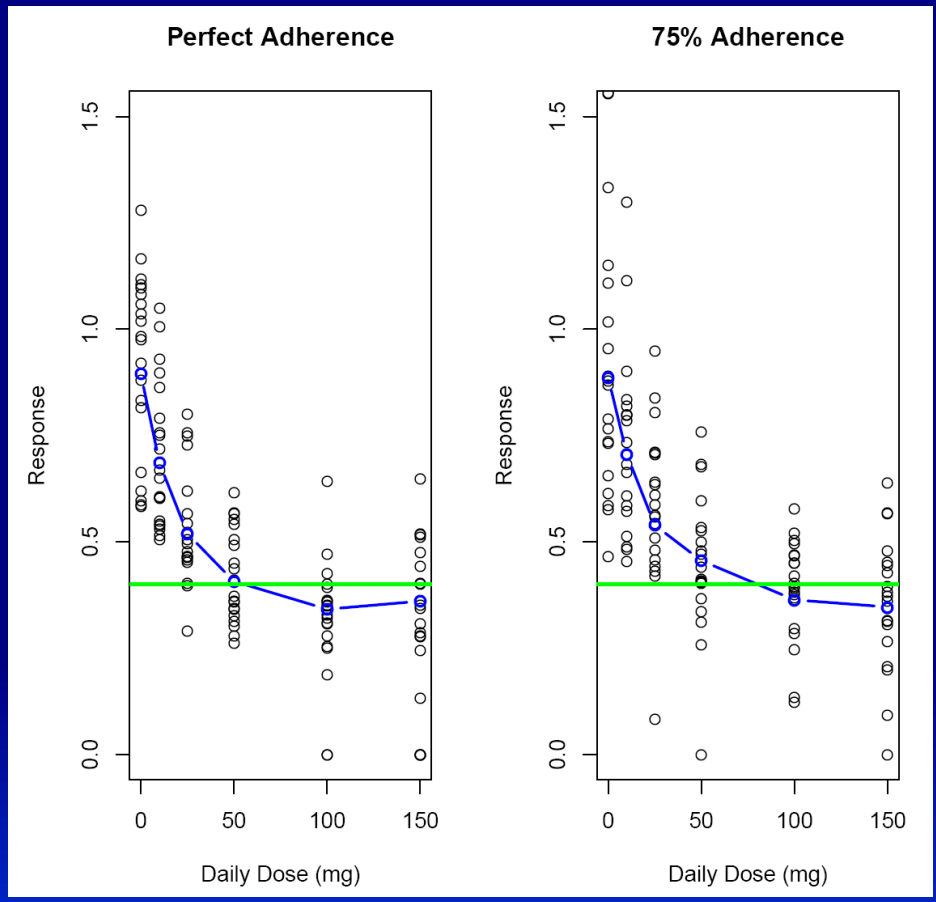




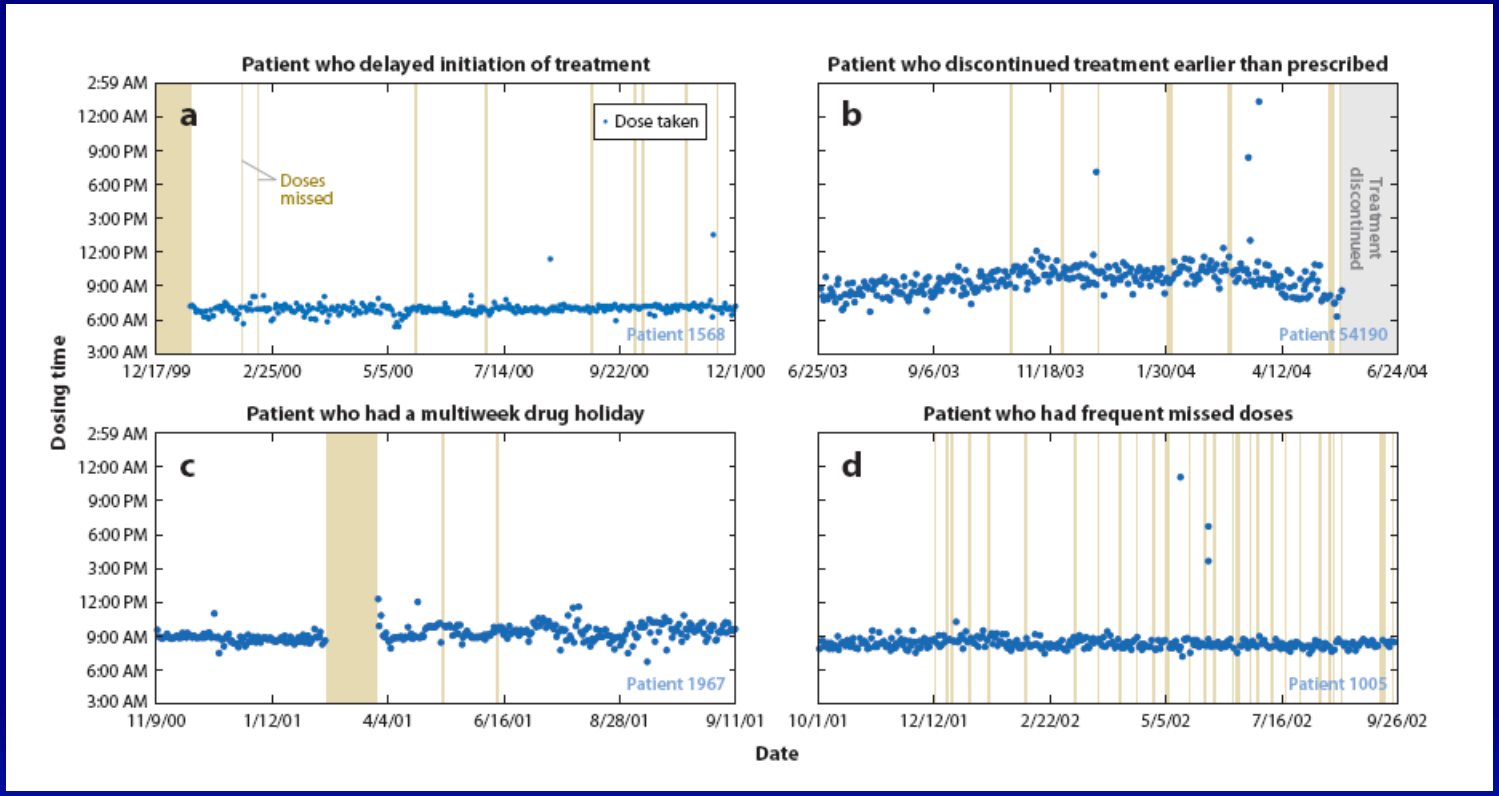
Shiovitz et al. JCP (2016) doi:10.1002/jcph.689

Practical Models for Simulating Non-Adherence

- One-Coin Model
  - P(missing dose$_i$) at each dosing time
  - Independent of status of previous dose
- ***Lower efficacy*** at all doses with non-adherence
- Choice of dose(s) to take forward ***greatly affected*** by adherence
  - 50 mg vs. 100 mg



In Reality, Adherence is not uniform, and may take on different patterns from patient to patient



Large gaps (“drug holidays”) often noted, which suggests that the degree of adherence depends on previous doses

Ann Rev Pharmacol Toxicol (2012) 52:275-301

Markov Model (Girard, 2005)

- P(taking today's dose) depends on whether you took yesterday's
  - Higher order models possible
- May tune model to give different profiles
  - May use covariates to allow for different responses

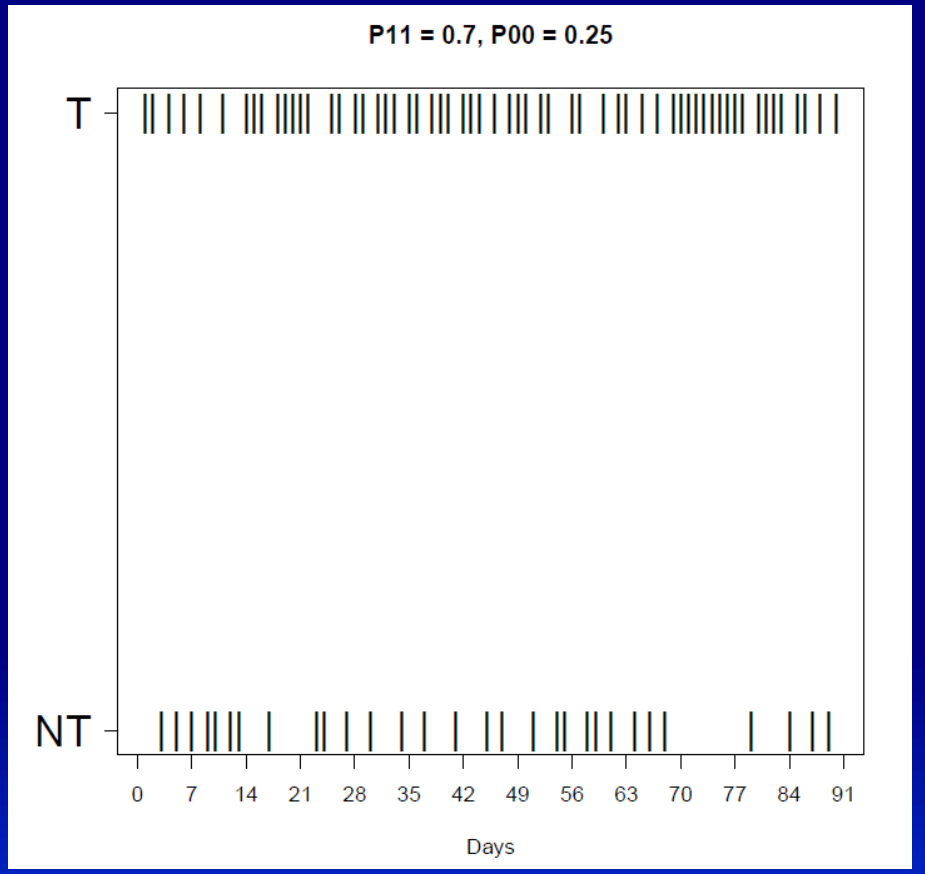
$$P_{00} = p(Y_i = NT | Y_{i-1} = NT)$$
$$P_{11} = p(Y_i = T | Y_{i-1} = T)$$

$$P_{01} = p(Y_i = T | Y_{i-1} NT) = 1 - P_{00}$$
$$P_{10} = p(Y_i = NT | Y_{i-1} = T) = 1 - P_{11}$$

Basic Clin Pharmacol & Toxicol 2005;96:228-234

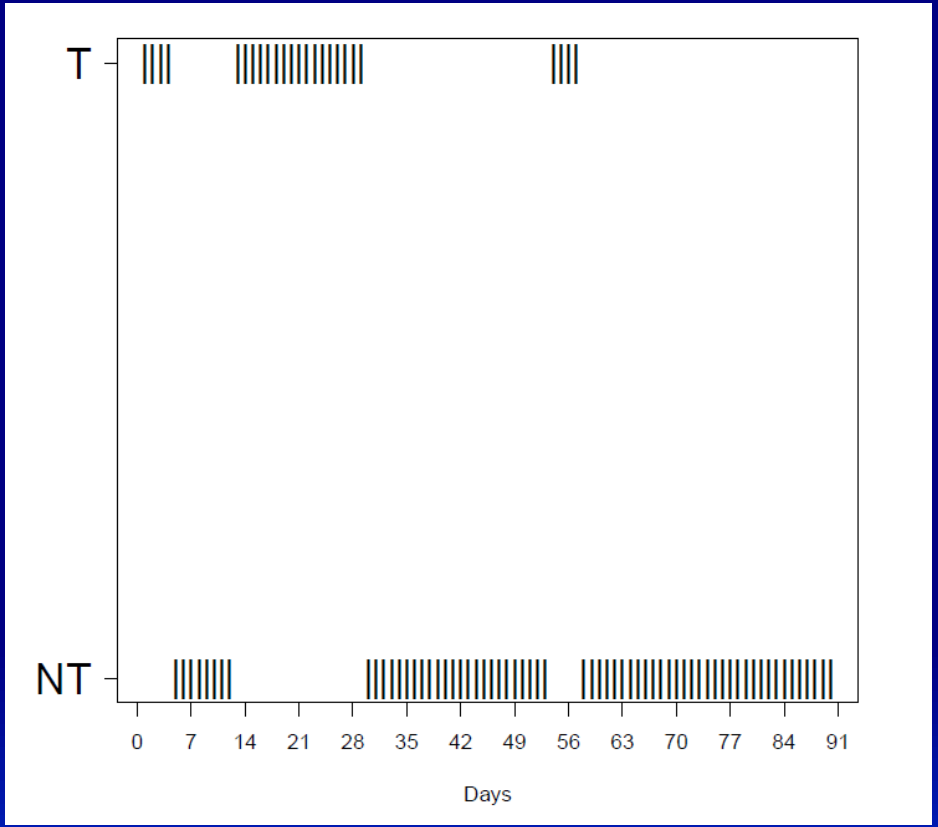
Example : Missing 2-4 doses/week

- P_{11}=0.7, P_{00}=0.25
- Runs of 2-10 doses, separated by shorter runs of non-adherence (1-2)
- May simulate the “week-end” effect – patients often less adherent on week-ends, due to less structured sleep, meal times



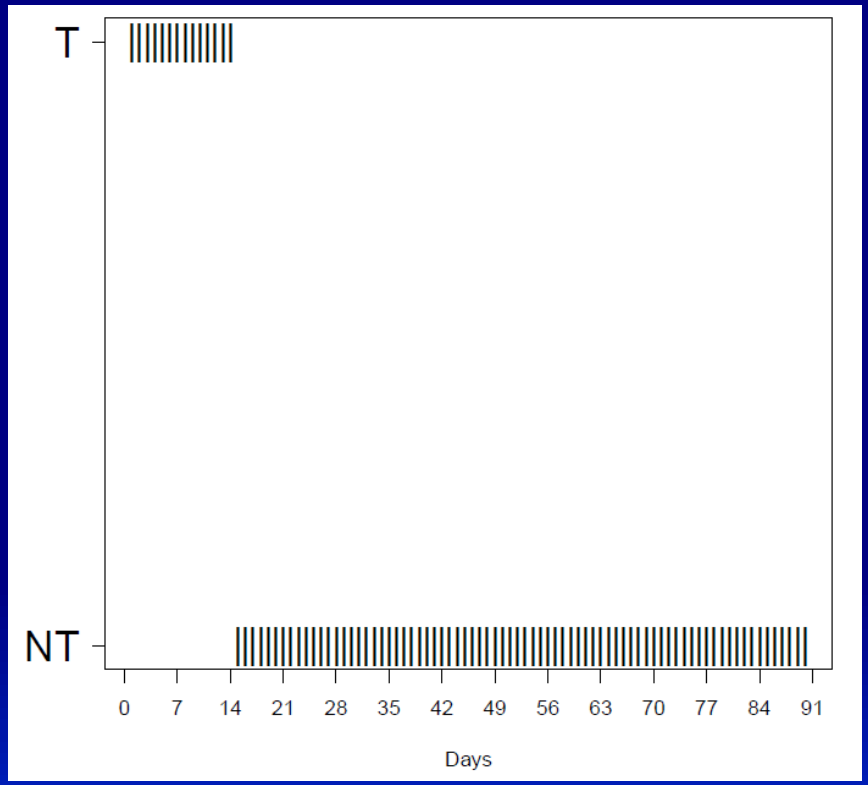
Example: Drug Holidays

- P_{11}=0.95, P_{00}=0.95
- Runs of adherence followed by long gaps
- May reflect behavior associated with access (e.g., getting refills)



Drop out

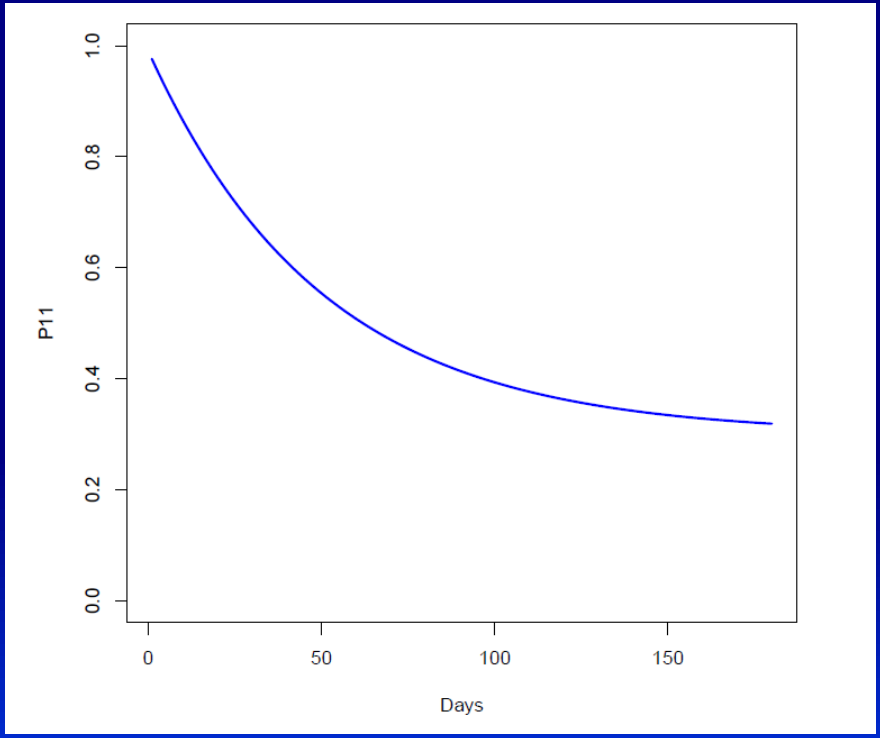
- P_{11}=0.95, P_{00}=1.0
- Perfect adherence for 2 weeks, then stop all medication
- In reality, studies will have a mix of these types of non-adherence in a study, so may need to consider mixture for simulation



Adherence may decrease with time

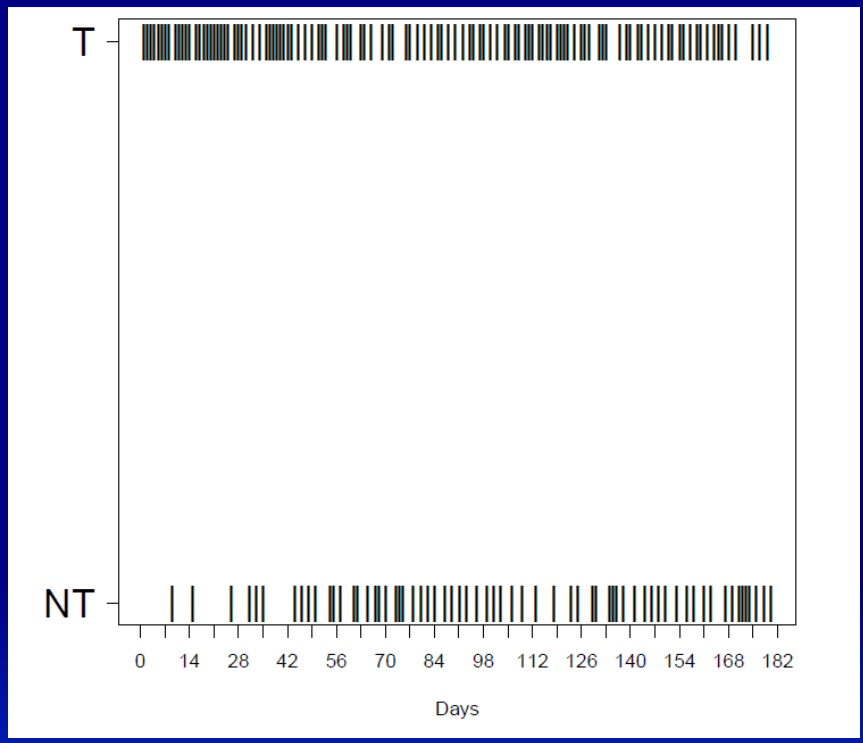
- Particularly with patients being treated for asymptomatic diseases
- May modify Markov model parameters to change over time
- Exact function used is empirical- could use others
- Could add lag-time
- Could study the effect of adherence interventions here, where parameters are “re-set” based on some intervention

$$P_{11}(t) = P_f - (P_f - P_i)e^{(-k*t)}$$



Decreasing P_{11} over time

- Density of T decreases with time, as expected
- Could also apply function to P_{00}, or to both, with different time-dependencies



There's more to Non-adherence than simply not taking medication

	Nature of protocol deviation	Type*	Candidate models to simulate protocol deviation
1	Patient is wrongly included (does not meet inclusion criteria)	D	Binomial/Multinomial
2	Less subjects than expected are included	C	Logistic
3	Patient receives the wrong treatment (e.g. placebo instead of active)	D	Binomial/ Multinomial
4	Patient receives the wrong dose	D	Binomial/ Multinomial
5	Patient crosses over to the alternate treatment	D	Binomial/Multinomial/Time to Event hazard model
6	Patient takes a forbidden comedication	D	Binomial/Multinomial
7	Patient takes fewer or extra dose(s) of treatment than prescribed, but the remaining doses are taken on time	D	Binomial/Multinomial or Markov
8	Patient takes all doses but does not take them on time	C	Normal or Uniform
9	Patient stops taking the treatment but remains on the study	D	Time to event hazard model
10	Patient or clinical team does not comply with measurement times, but all measurements are recorded	C	Normal or Uniform
11	Patient or clinical team misses some measurements but completes the study	D	Binomial/ Multinomial or Markov
12	Measurements are incorrect and though missing (deficient measurement technique)	D/C	Binomial/Multinomial+Normal or Uniform distributions
13	Measurement times are switched	D	Binomial/Multinomial
14	Patient drops out before the end of the study	D	Time to event hazard model

*C: Continuous deviation from protocol.
D: Discrete deviation from protocol.

Girard, 2005

Simulating Non-adherence

- Simplification is absolutely necessary
- A mixture of different “types” of non-adherence may be more realistic, but must keep things tractable
- Might be more useful to simulate just one or two types, then see which type has the greater effect
- Sensitivity analysis around different levels of NA is a must
- ***Any simulation of non-adherence is better than assuming it does not exist***

What is the biggest barrier to a strategy of accounting for non-adherence in clinical trials?

"One underlying assumption that the author is making is that if patient adherence were better quantified and factor in as a covariate in appropriate analyses, clinical trial outcomes would improve. But intent-to-treat is not going away since regulators are interested in what treatment will look like in the real world. If adherence is poor in a clinical trial, it is likely worse in the real world, and regulators are loath to approve treatments that will fail in the real world."

- Why should anyone involved in drug therapy (clinicians, payors, industry) be satisfied with the status quo?
- ITT ≠ pre-specified stratification by level of adherence
- The FDA is on record as supporting the quantification of adherence, see ***Guidance for Industry: Enrichment Strategies for Clinical Trials to Support Approval of Human Drugs and Biological Products***

Modeling Non-Adherence

- Not often done – relatively few examples in the literature
  - Lack of data
- Can get very complex – an ill-conditioned problem
  - Simplification is a must
- Often lack the data to do this well
- May be very helpful in elucidating ways to improve adherence

Markov mixed effects modeling using electronic adherence monitoring records identifies influential covariates to pre-exposure prophylaxis

Kumpal Madrasi[1,a], Ayyappa Chaturvedula[1,7], Jessica E. Haberer[2], Mark Sale[5], Michael J. Fossler[4], David Bangsberg[2], Jared M. Baeten[6], Connie Celum[6], Craig W. Hendrix[3]

- Electronic Adherence records from the Partners PrEP study used for the analysis
  - Sub-set of 4,747 HIV uninfected members of serodiscordant couples from nine clinical research sites in Kenya and Uganda were followed in the clinical trial
- One coin and 1st-3rd order Markov models fit to data using NONMEM
- Covariates investigated include basic demographics, number of sex partners, alcohol use, polygamy

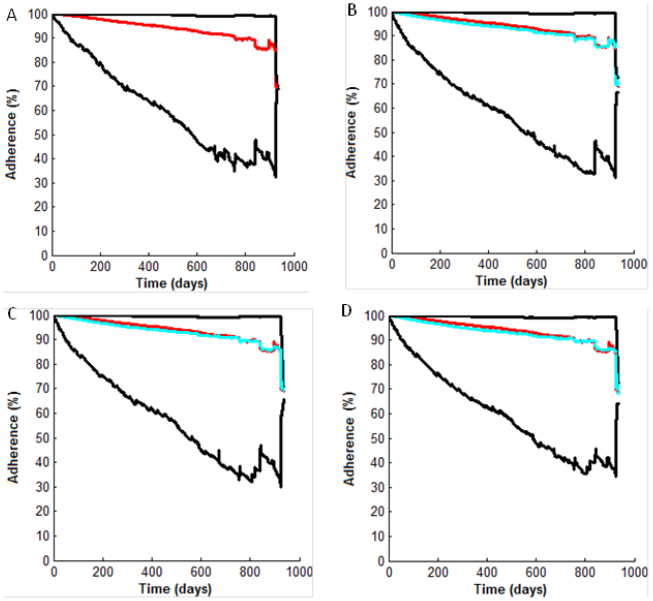
Results

Model	Number of Parameters	OFV	AIC
1 coin model	2	368004.3	368008.3
1st order Markov model	4	318218.5	318226.6
2nd order Markov model	8	303370.4	303386.4
3rd order Markov model	16	300883.9	300915.9

- 3rd order Markov model fit best
- 4x parameters

Very little Difference among the 3 Markov Models in predicting adherence over time

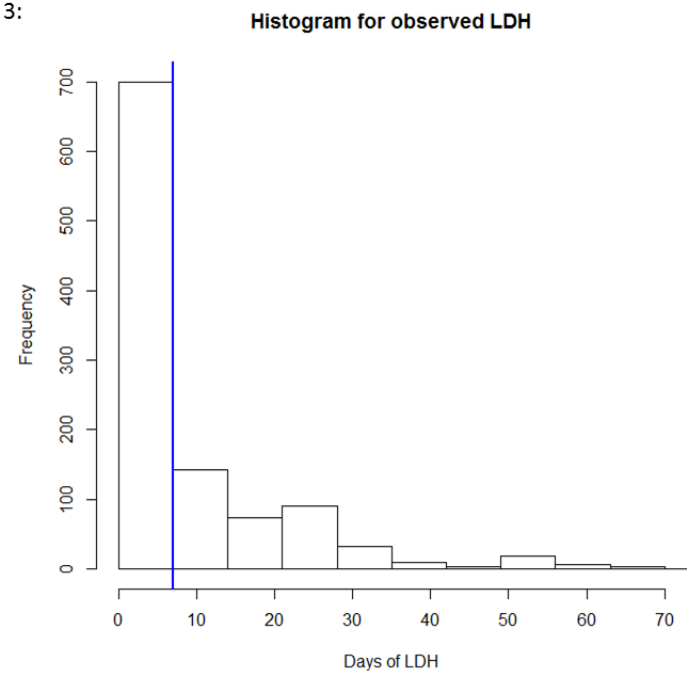
Figure 1:



Red line – observed adherence, blue – prediction, black 90% CI

First Order Model does a reasonable job of predicting the longest drug holiday (LDH)

Figure 3:



Covariates

Parameter	Estimate	RSE(%)
P_{01} (positively correlated with adherence)	0.7	1.8
P_{10} (negatively correlated with adherence)	0.067	5.5
Effect of no sex on P_{01}	-0.14	20.8
Effect of sex with partner other than study partner on P_{10}	0.4	14.14
Effect of sex with partner other than study partner on P_{01}	-0.13	36.9
Effect of no sex on P_{10}	0.18	19.94
Effect of female gender on P_{10}	-0.6	12.18
Effect of youth on P_{10}	0.51	18.73
Effect of sex with other partner and study partner on P_{01}	0.056	43.61
Effect of weekend on P_{01}	-0.036	24.45
Effect of weekend on P_{10}	0.063	28.75

- Lower adherence after abstinence, sex with other partner(s), gender, age (lower in ages 19-28), and weekends

Conclusions

- Markov models of adherence can be used to predict adherence patterns at an individual level to design customized interventions
- When linked with antiretroviral pharmacokinetic and viral dynamic models could provide an *in silico* tool to calculate a threshold adherence required for drug efficacy

Overall Conclusions

- Adherence is the most important covariate in any clinical trial
  - Despite this, we seldom take adherence into account when designing studies and analyzing clinical data
- My plea
  - Push for adherence measures in all P2 and P3 trials
  - Include adherence in analysis of data
  - ***Include adherence in simulations***