Population Pharmacokinetics of Atazanavir in Naïve HIV-Infected Patients using Medication Events Monitoring System (MEMS) for drug intake timing

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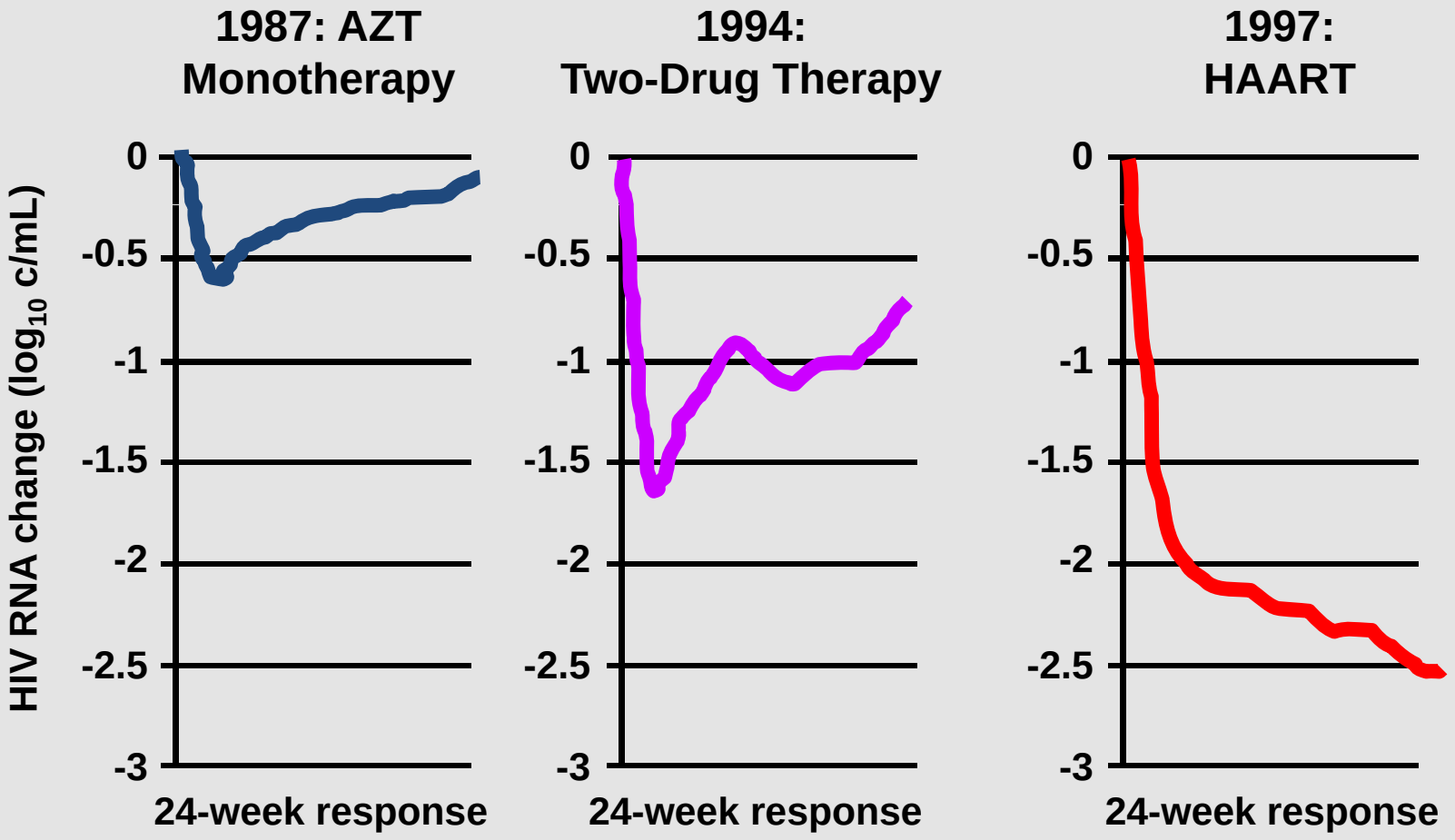
Antiretroviral Activity: A Historical Perspective



Fischl, *NEJM,* 1987
Hamilton, *NEJM*, 1992

Eron, *NEJM,* 1995;
Hammer, *NEJM,* 1996

Gulick, *NEJM,* 1997;
Cameron, *Lancet,* 1998

Atazanavir Profile

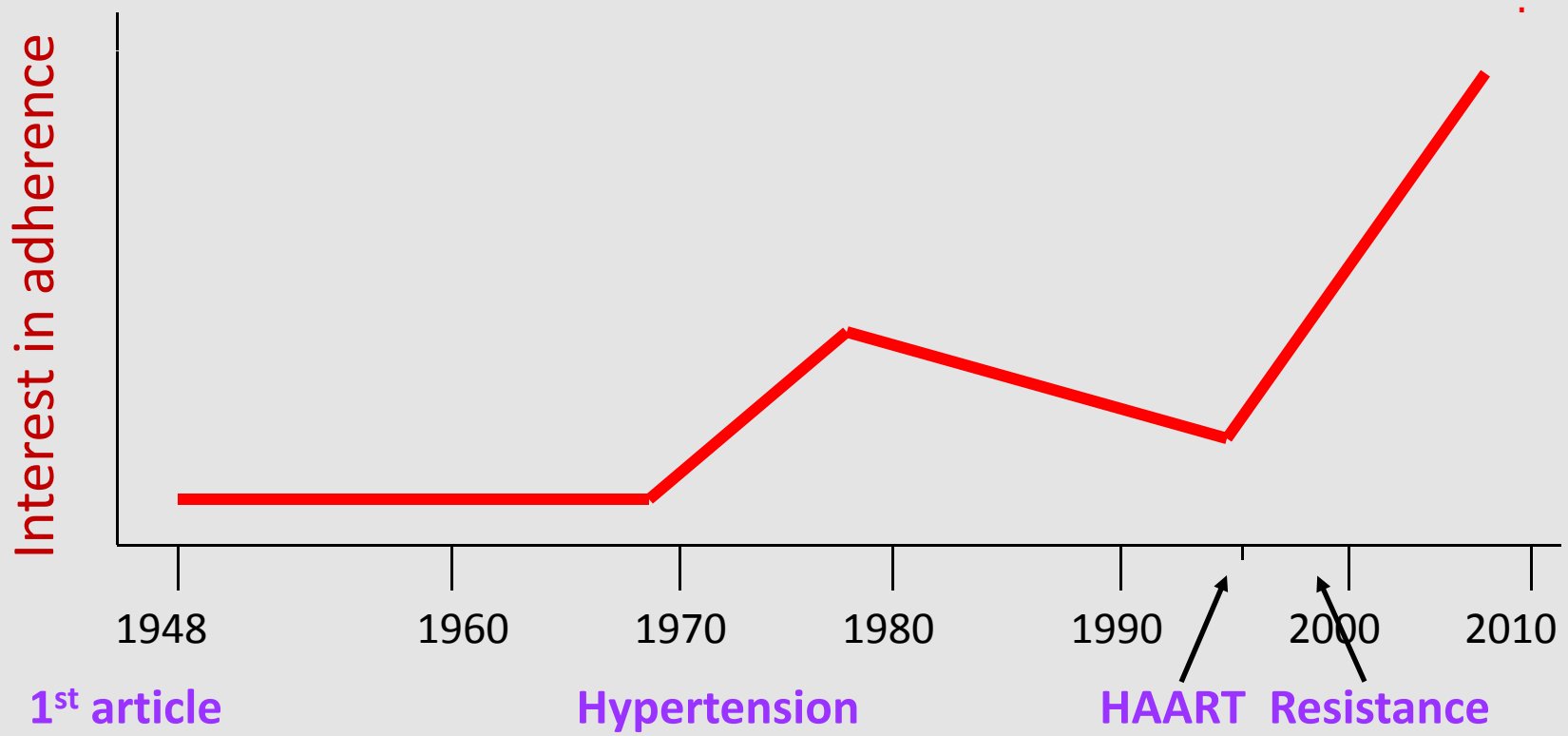
- ✓ Inhibitor of HIV protease
- ✓ Favorable potency and resistance profile
- ✓ Distributes widely (CSF, semen)
- ✓ Metabolized via CYP3A4
- ✓ Favorable oral bioavailability (> 50%)
- ✓ Increased absorption in fed state
- ✓ Prolonged $t_{1/2}$ – allows for QD dosing

- ✓ Dose regimens:
  - 300mg QD boosted with 100mg ritonavir
  - 400 mg QD with food (2 capsules)


THE AIDS CRISIS
IS NOT OVER

Adherence: "It's Everything" (WHO)

- ✓ Patients on therapy do not benefit if they don't take medicine
- ✓ Resistance develops, harming persons on therapy and others
- ✓ Resources wasted

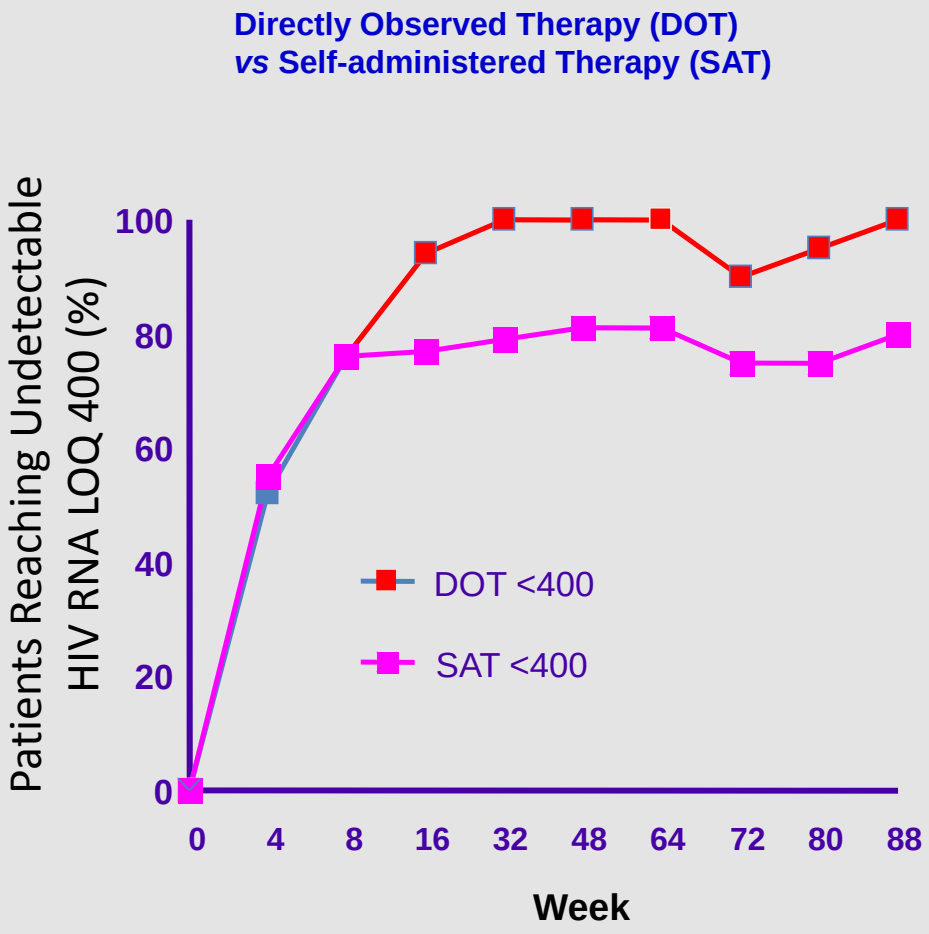


Hardy MC. JAMA

Hecht et al. N Engl J Med 1998;339:307

HIV Medication is Highly Effective When Taken as Directed

- ✓ Directly Observed Therapy vs. Self-administered Therapy in prison inmates
- ✓ 100% of patients in the Department of Corrections (n=42) who took all pills on time every day had an undetectable viral load by 32 weeks and out to 88 weeks



Fischl. 8th CROI; 2001; Chicago. Abstract 528

Aims:

I. To describe **pop PK of atazanavir** using accurate patient dosing-histories

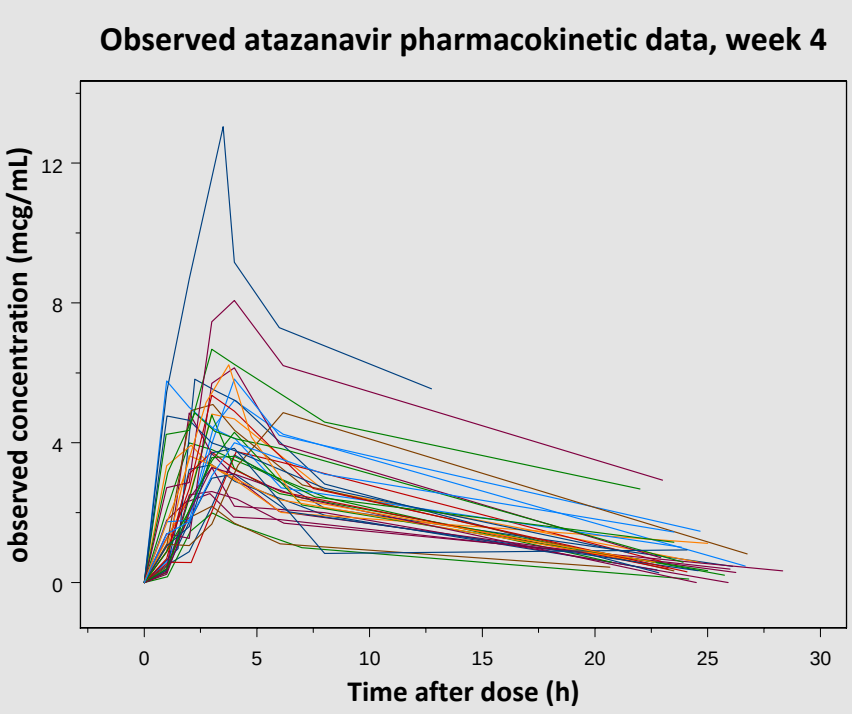
II. To demonstrate how different **adherence assumptions** may impact the population PK analysis outcomes

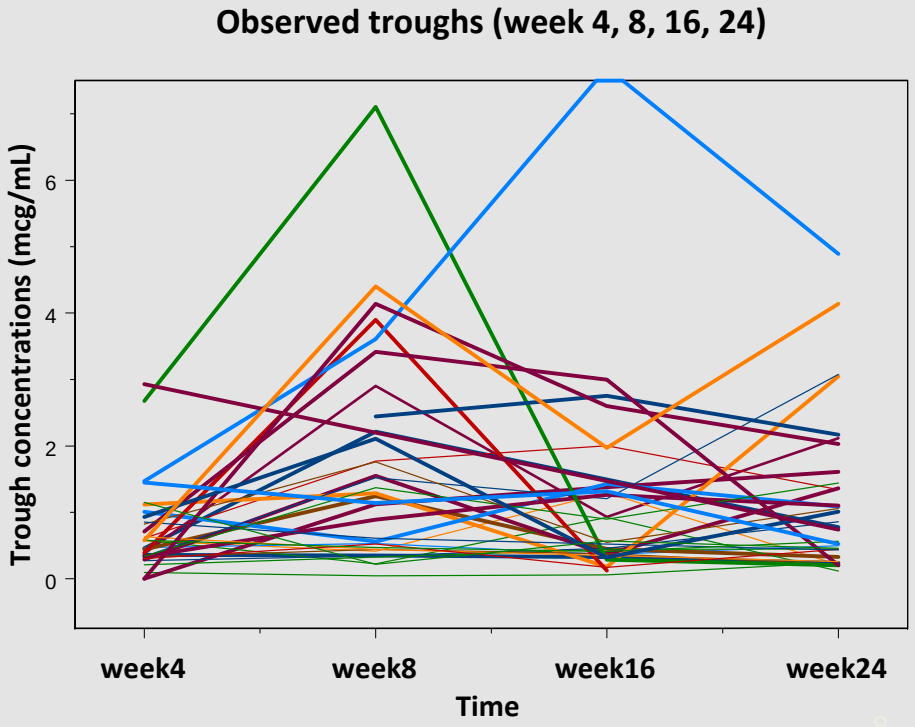
III. To develop **ritonavir Pop PK** model

IV. To **link ritonavir and atazanavir PK (ongoing work)**

Cophar 3-ANRS134 trial

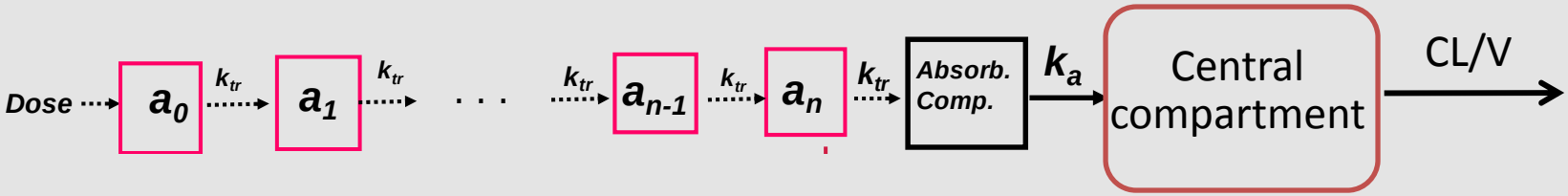
- ✓ Sponsor: Agence Nationale de Recherche sur le Sida (ANRS)
- ✓ 35 HIV-1 infected patients followed for six months
- ✓ Baseline plasma viral load value > 1000 copies/ml and naïve of PI
- ✓ Initiating a treatment containing one protease inhibitor (PI) Atazanavir with ritonavir and two nucleoside analogs (NRTI): Tenofovir and Emtricitabine

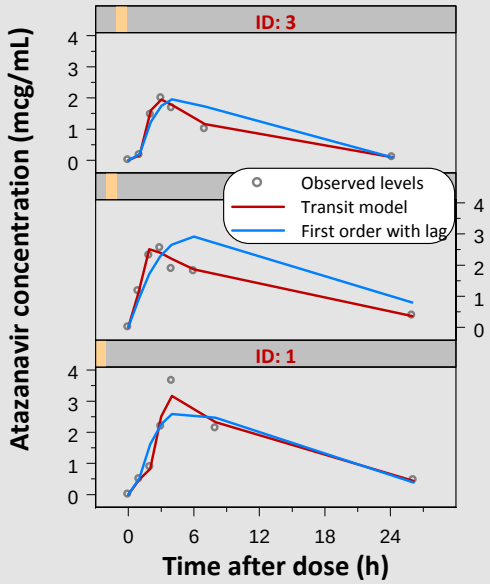




(i) Population PK model atazanavir

Transit compartment model





Comparison of differenet absorption models

Model	-2 x log Likelihood	Δ OFV*	RV (%)	# of PK parameters
Zero order	328	208	48	6
First order	267	147	41	6
Sequential Zero-First order	200	80	31	9
First order with a lag time	184	64	29	8
Transit compartment model	120	0	18	10

*Comparison to the Transit compartment model, RV=residual variability

Major findings:

- ✓One compartment disposition model
- ✓Improved absorption model (Transit compartment model)
- ✓Better description of Cmax and absorption delay
- ✓Better description of exposure in general

(ii) Influence of adherence assumption on Pop PK outcome

- ✓ All drugs were supplied in bottles with a MEMS cap
- ✓ Full dosing history available for all patients
- ✓ Dairy data where patients report any deviations from MEMS recorded drug intake (drug holiday)

Medication

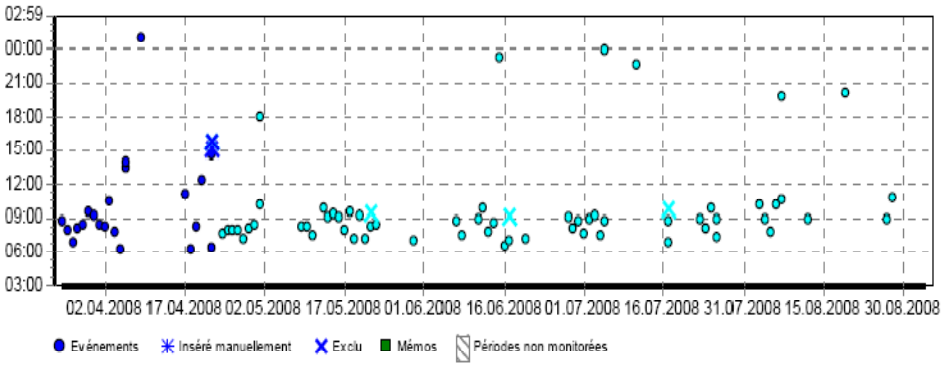
Events

Monitoring

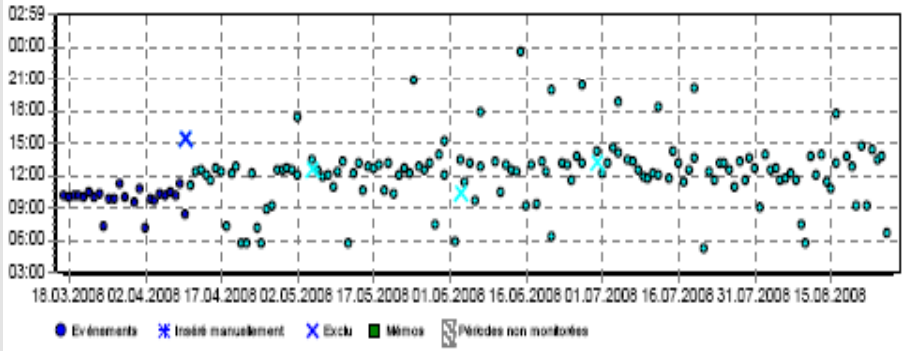
System

Adherence data, example of 2 patients

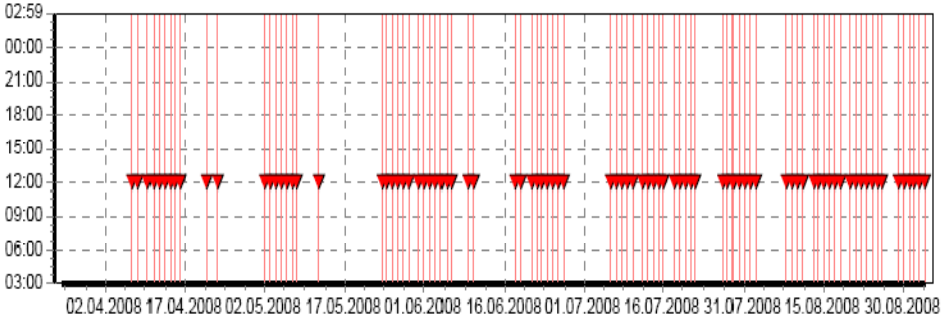
Dosing history: A



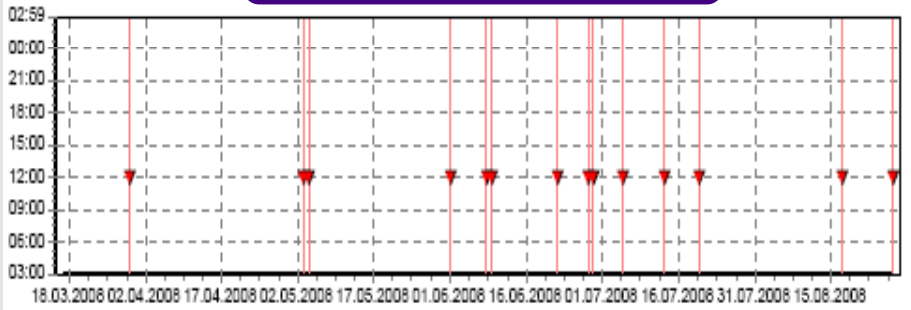
Dosing history: B



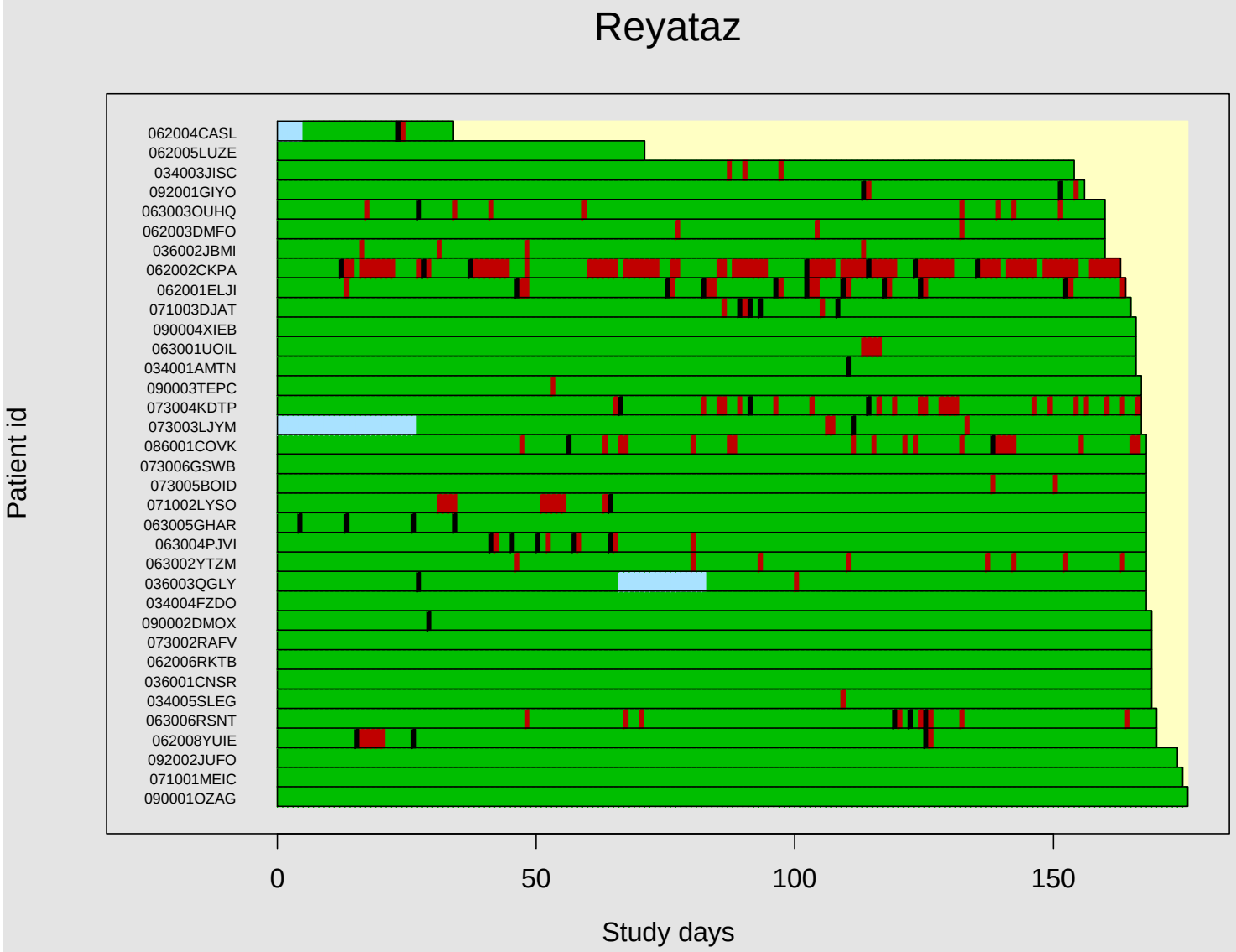
Missed doses: A



Missed doses: B



Adherence, atazanavir heat map



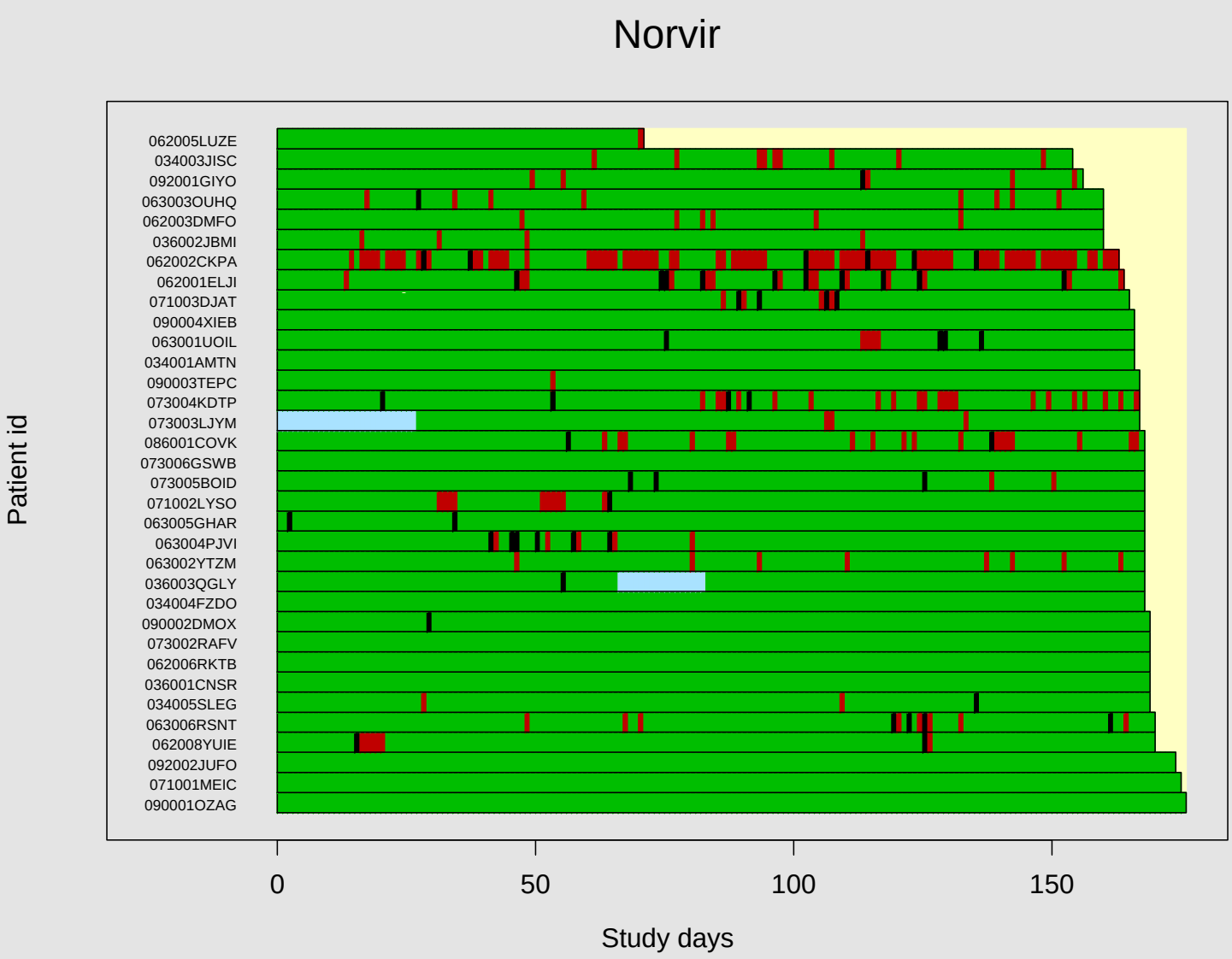
no dose

correct intake

overdosing

non-monitored

Adherence, ritonavir heat map



no dose

correct intake

overdosing

non-monitored

Adherence objective

- ✓ To study how underlying dosing-history assumptions affect atazanavir PK model outcomes

- ✓ Variables of interest:
  - Inter-individual variability
  - Inter-occasion variability
  - Residual variability

Adherence assumptions:

(I) Assuming steady state:

- ✓ all patients are at steady state (SS) and the last reported time of dose intake by the patient before a PK visit is accurate
- ✓ Assuming full compliance

(II) Full MEMS data:

- ✓ full dosing-histories as recorded by MEMS are exact

(III) ”Reliable” MEMS data – GOLD standard

- ✓ ”reliable” dosing-history data consists only of MEMS records concordant (within 3 hours) with last reported time of dose intake before each PK visit

Adherence results

PK Parameters	$\mathcal{A}_{ss}$:SS assumption	$\mathcal{A}_{MEMS}$:Full MEMS	$\mathcal{A}_{GOLD}$:Gold standard
	Parameter estimates (RSE)		Final parameters
CL/F (L/h)	7.2 (4.4)	6.8	6.9 (8.1)
V/F (L)	79.2 (8.9)	**102**	81.1 (6.8)
ka (h^{-1})	2.7 (26.8)	5.6	3.2 (42.1)
MTT (h)	1.3 (11.2)	1.5	1.35 (11)
NN	17.3 (46.7)	8	11.5 (26.4)
IIV (CL/F)*	47.4 (28.7)	44.3	40.2 (32.7)
IOV(CL/F)*	26.5 (16.9)	**<1**	**<1**
IIV (V/F)*	30.0 (43.2)	61.4	30.1 (28.5)
IIV (ka)*	73.5 (47.2)	120	78.4 (73.2)
IIV (MTT)*	47.4 (28.7)	40.1	45.2 (31.8)
RV (week 4)*	18.7 (16.9)	**27.7**	19.4 (15.5)
RV (> week 4)*	38.0 (33.1)	**47.4**	43.4 (10.6)

Adherence assumption findings:

(I) Assuming steady state:

- ✓ Give rise to significant inflated **inter-occasion variability in Clearance**

(II) Full MEMS data:

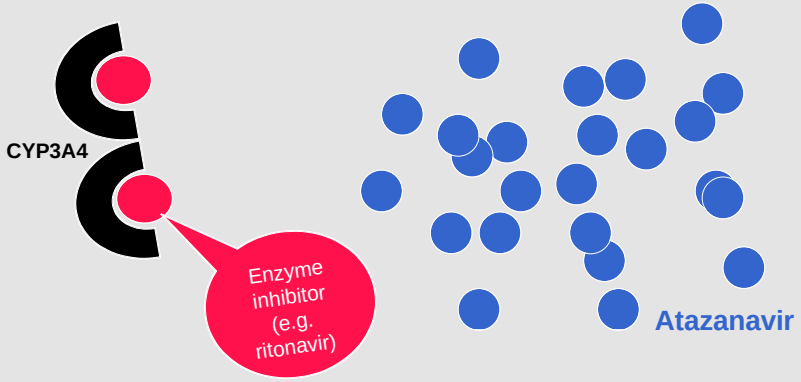
- ✓ **Inter-occasion** varability in CL is not present any more
- ✓ Biased parameter estimate (Vd)
- ✓ Numerical difficulties

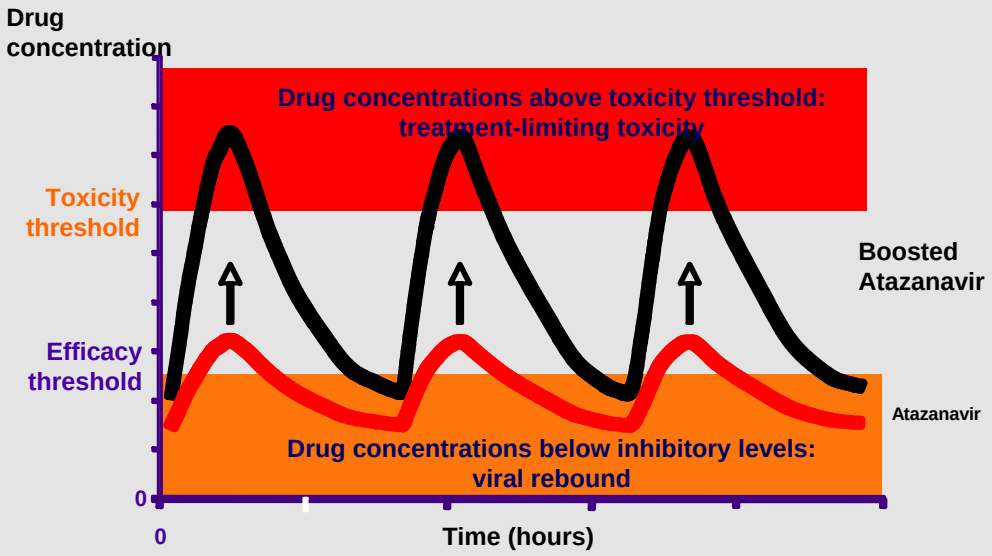
(III) ”Reliable” MEMS data – GOLD standard

- ✓ Good parameter estimates
- ✓ Low variability
- ✓ Stable numerical properties

Interaction between atazanavir - ritonavir

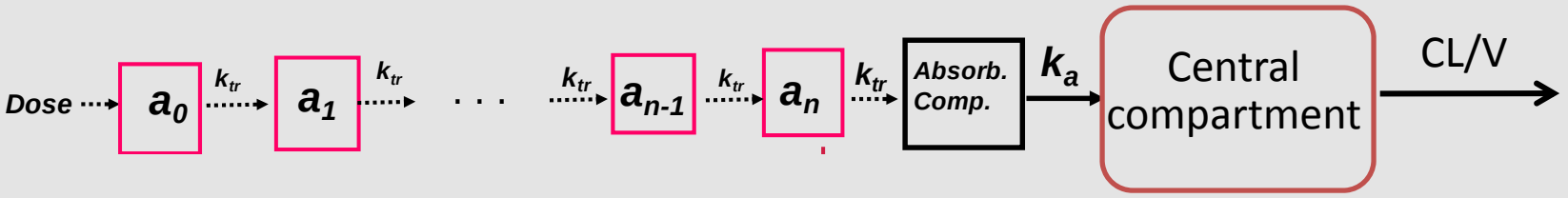
- ✓ All PIs are metabolized by the CYP3A4 enzyme system
- ✓ All PIs can inhibit CYP3A4 enzymes
  - Ritonavir most potent inhibitor





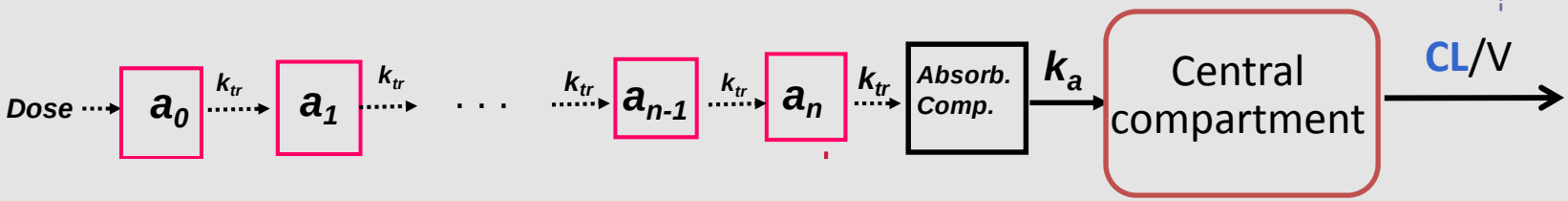
Link atazanavir – ritonavir PK

Ritonavir



$$CL_{ataz} = CL_0 \cdot \left(1 - \frac{E_{max} \cdot Exps_{rito}}{Exps_{50} + Exps_{rito}}\right)$$

Atazanavir



Initial Insights on ritonavir – atazanavir link

$$CL_{ataz} = CL_0 \cdot \left(1 - \frac{E_{max} \cdot Exps_{rito}}{Exps_{50} + Exps_{rito}}\right)$$

CL_0=43.6 L/h (uncertain)

E_{max}=0.961 (high)

$Exps_{50}$=1.38 mg.h/L (low)

- ✓ Limited data to support estimation of CL_0
- ✓ Difficulties to link via ritonavir concentration
- ✓ Saturated boosting

Ongoing & future work

- ✓ Pharmacogenetics & other covariates
- ✓ NRTI
- ✓ Complete interaction model
- ✓ Viral load and CD4 analysis
- ✓ Toxicity analysis

Final Conclusions

- Improved population PK model of atazanavir (absorption)
- Assuming steady-state gives rise to inter-occasion variability in CL
- Raw MEMS data needs to critically be assessed
- A new model together with MEMS dosing histories allows us to precisely assess :
  - ✓ individual exposure,
  - ✓ cumulative individual exposure,
  - ✓ time above MIC,
  - ✓ Atazanavir concentration at any time point

which is **essential information** for understanding **individual virological response and potential success/failure of the therapy**

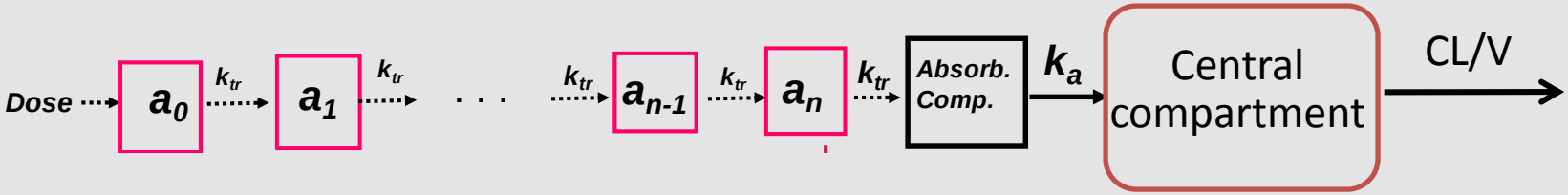
Acknowledgments

- ✓ All patients that have participated in this study
- ✓ Terry Blaschke and John Urquhart
- ✓ IF: stiftelse (Grant sponsorship)

BACK UP SLIDES

(III) Population PK model ritonavir

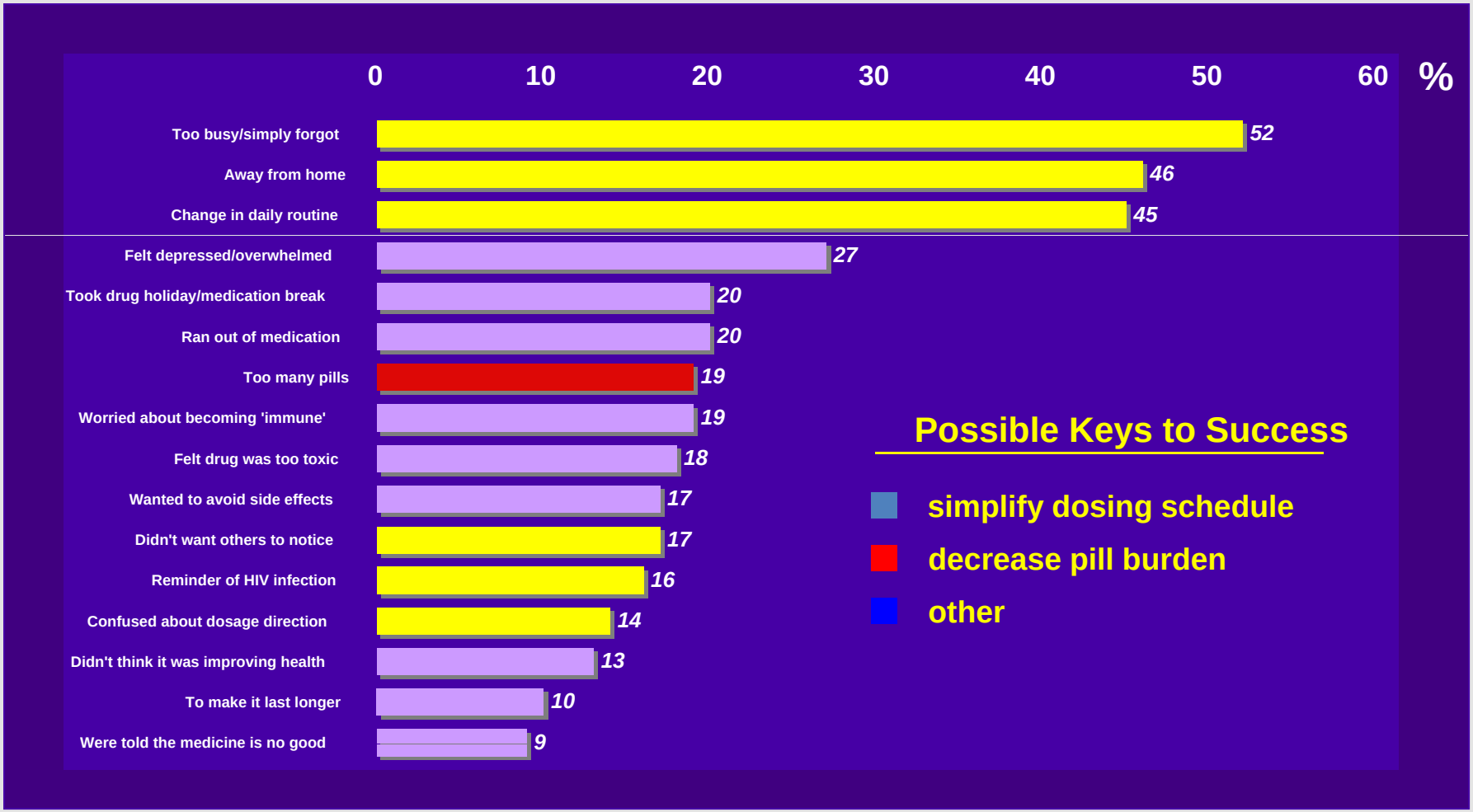
Transit compartment model



Major findings:

- ✓ One compartment disposition model
- ✓ However evidence of peripheral cmpt
- ✓ Improved absorption model (Transit compartment model)
- ✓ Better description of Cmax and absorption delay
- ✓ Better description of exposure in general

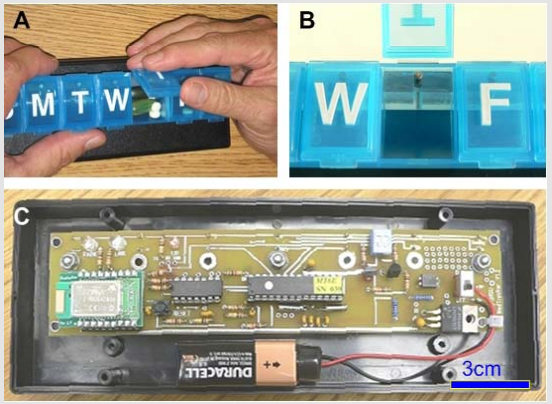
Why Isn't HIV Medication Always Taken As Directed?



Adapted from: Gifford AL et al. JAIDS 2000; 23: 386-395

Different Measures of Adherence
There is no "gold standard"

- ✓ Self-reported
  - Self-administered
  - Interviewer-administered
- ✓ Pill count
  - Announced? Unannounced?
- ✓ Pharmacy refill
- ✓ Electronic Monitoring Devices (EDM), e.g., Medication Event Monitoring System (MEMS)
- ✓ Patient diary
- ✓ Adherence helper diary
- ✓ Visual analogue scale
- ✓ Etc.



MEMScaps, Aardex Corp.