

Mathematical-Statistical Modeling to Inform the Design of HIV Treatment Strategies and Clinical Trials

2007 FDA/Industry Statistics Workshop

Marie Davidian*
Department of Statistics
North Carolina State University



<http://www.stat.ncsu.edu/~davidian>

** Joint work with H. Thomas Banks (NCSU) and Eric S. Rosenberg (MGH and Harvard Medical School)*

Outline

- Objectives
- HIV therapy and structured treatment interruption (STI)
- HIV dynamic models and control
- Mathematical-statistical framework
- Design of a clinical trial in acute-infection
- Next steps - design of STI strategies
- Closing remarks

Objectives

- Describe a *multidisciplinary collaboration* supported by a 5-year grant from NIAID
- *Main players*: Applied mathematician/control theorist, immunologist/infectious disease clinician, and *statistician*
- Use *mathematical-statistical modeling of disease progression* and *simulation* to design HIV treatment strategies and clinical trials to study them
- Focus on *better use of existing antiretroviral therapies (ART)* to manage HIV infection *over time*
- Design and carry out a *clinical trial* assisted by modeling and simulation
- Collect *extensive data* to inform *refined modeling* \implies more sophisticated strategies and trials

HIV therapy and STI

Potent ART for treatment of HIV-1 infection:

- Has led to *profound decrease* in morbidity and mortality from HIV and AIDS-related illnesses . . .
- . . . but *cannot* completely eradicate the virus \implies need for *life-long* treatment
- *Complications* – side effects, toxicities, adherence issues, cost, burden, development of drug resistance, life style issues, . . .
- \implies Continuous treatment *impossible* for most patients

HIV therapy and STI

Result: *Structured* (or *supervised*) *treatment interruption* (*STI*)

- ART for some period of time followed by *interruption* and *possible re-initiation*, perhaps through *several cycles*
- *Non-adaptive* (*non-dynamic*) strategies – planned *advance*, e.g., cycles of 8-weeks-on/8-weeks-off
- *Adaptive* (*dynamic*) strategies – decisions to interrupt and re-initiate based on *rules* taking patient information as input, e.g., stop or start based on *CD4+ T cell count* or *viral load*
- *Goals* – maintain *viral suppression*, preserve *immune response*, lower viral load “*set point*”

HIV therapy and STI

Rationale: Hypotheses

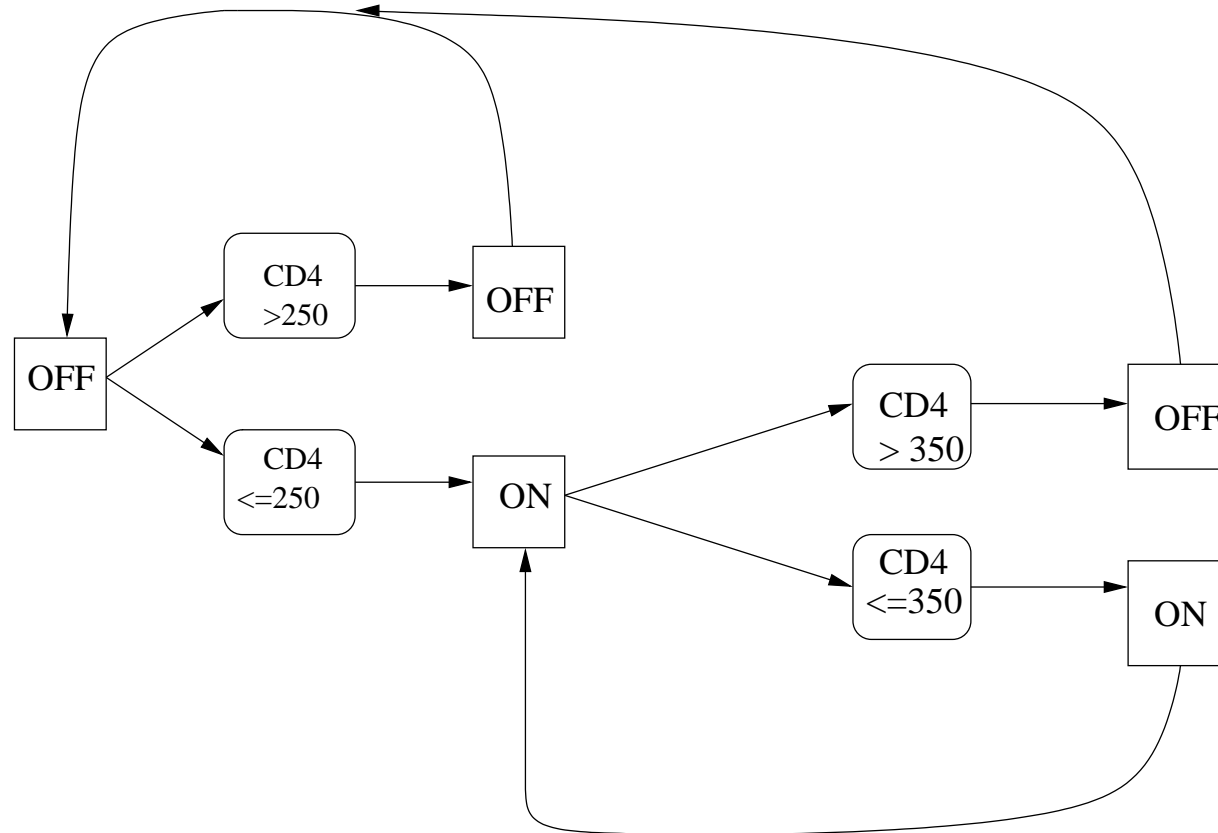
- *Chronic infection* – relieve *burden* and *side effects*; allow *wild-type virus* to *repopulate* in subjects with *drug resistance*
- *Acute infection* – preserve *HIV-specific immune response* and allow *discontinuation* of ART; on-off cycles serve as “*self-vaccination*” further stimulating immune response

Studies so far: *Mixed* results, e.g.,

- CPCRA “*Strategies for Management of Antiretroviral Therapy*” (*SMART*) trial (El-Sadr, Neaton, et al., 2006) in *chronically-infected* subjects
- Compared *continuous ART* to an *adaptive STI strategy* (“*drug conservation*”) – on-off ART dictated by *CD4+ T cell count*

HIV therapy and STI

Drug conservation strategy in the SMART study:



Result of SMART: Stopped *early* (~ 5500 pts), drug conservation
⇒ 2x risk of primary endpoint (AIDS or death)

HIV therapy and STI

Our premise: Strategies so far may have been *unfortunately chosen*

- Based on “*educated guesses*” *expert opinion*, pieced-together *clinical evidence*
- E.g., CD4+ thresholds in SMART chosen after *much debate* among experts...
- ...and *decision rules* did not include *viral load* (or other info)
- \implies it is *premature* to dismiss STI and *adaptive treatment strategies*
- A formal, *evidence-based* approach combining *biological knowledge*, *data* in a *principled* way is needed to *design* strategies

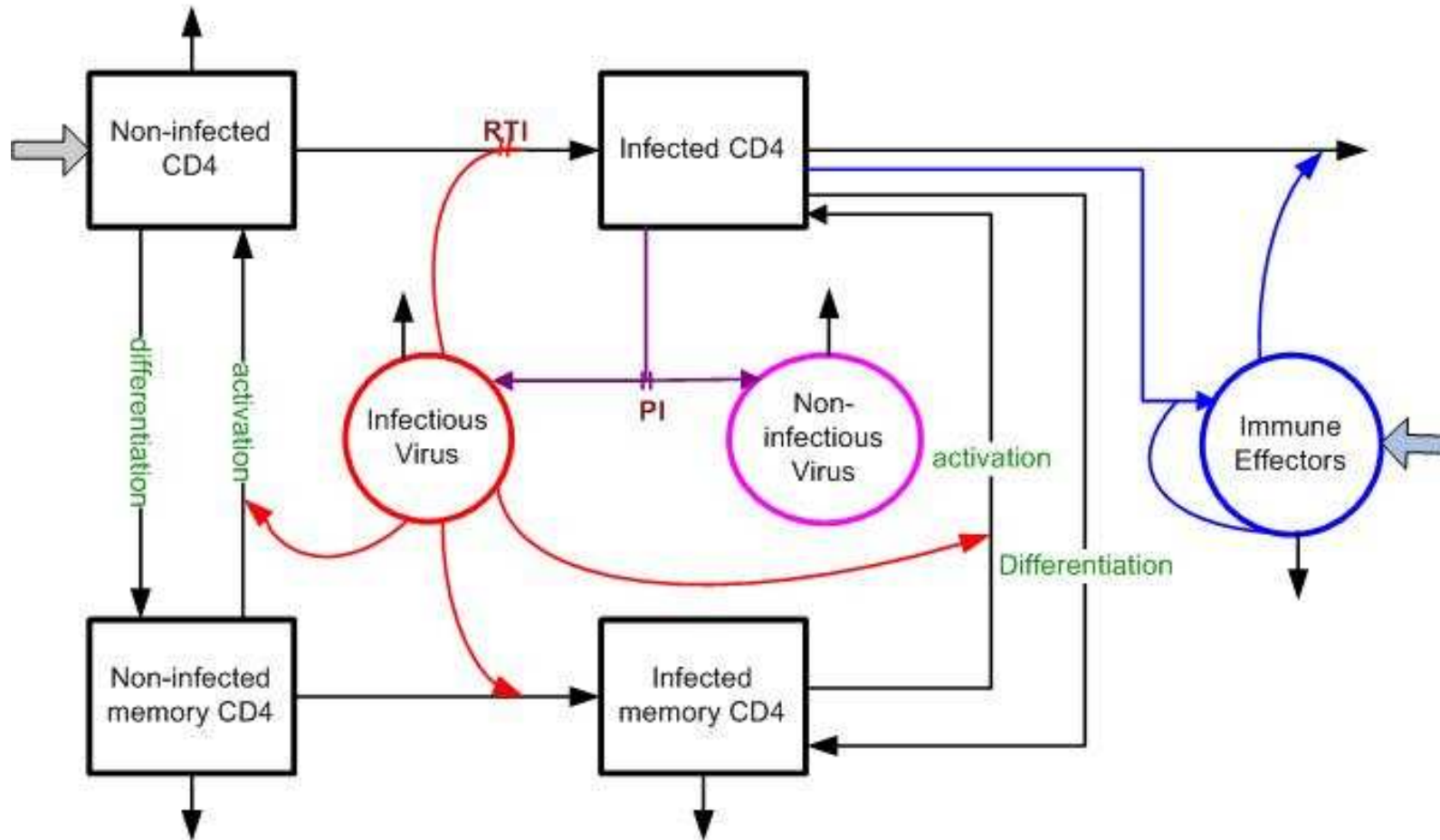
HIV dynamic models and control

HIV dynamic models:

- Represent *mathematically* known and hypothesized *mechanisms* involved in the *virus-immune system* interaction taking place *within a single subject*
- Series of “*compartments*” characterizing different populations of virus and constituents of the immune system
- Interactions among compartments described by a system of (*deterministic*) *nonlinear ordinary differential equations*
- \implies In principle, *viral load*, *CD4+ T cell count*, etc, at any time

HIV dynamic models and control

Possible model for within-subject dynamics:



HIV dynamic models and control

Model for within-subject dynamics: $s = 7$ “states”

$$\begin{aligned}\dot{T}_1 &= \lambda_1 - d_1 T_1 - \{1 - \epsilon_1 u(t)\} k_1 V_I T_1 \\ \dot{T}_2 &= \lambda_2 - d_2 T_2 - \{1 - f \epsilon_1 u(t)\} k_2 V_I T_2 \\ \dot{T}_1^* &= \{1 - \epsilon_1 u(t)\} k_1 V_I T_1 - \delta T_1^* - m_2 E T_1^* \\ \dot{T}_2^* &= \{1 - f \epsilon_1 u(t)\} k_2 V_I T_2 - \delta T_2^* - m_2 E T_2^* \\ \dot{V}_I &= \{1 - \epsilon_2 u(t)\} 10^3 N_T \delta (T_1^* + T_2^*) - c V_I - \{1 - \epsilon_1 u(t)\} \rho_1 10^3 k_1 T_1 V_I \\ &\quad - \{1 - f \epsilon_1 u(t)\} \rho_2 10^3 k_2 T_2 V_I \\ \dot{V}_{NI} &= \epsilon_2 u(t) 10^3 N_T \delta (T_1^* + T_2^*) - c V_{NI} \\ \dot{E} &= \lambda_E + \frac{b_E (T_1^* + T_2^*)}{(T_1^* + T_2^*) + K_b} E - \frac{d_E (T_1^* + T_2^*)}{(T_1^* + T_2^*) + K_d} E - \delta_E E\end{aligned}$$

- $\theta = (\lambda_1, d_1, \epsilon_1, k_1, \dots)^T$ plus initial conditions
- Observable: *CD4 count* = $T_1 + T_1^*$, *viral load* = $V_I + V_{NI}$
- $u(t)$ = ART input at t ($0 \leq u(t) \leq 1$, 0 = off, 1 = on)

HIV dynamic models and control

In general: HIV dynamic model with s states

$$\dot{x}(t, \theta) = g\{t, x(t, \theta), \theta\}, \text{ solution } x(t, \theta) \text{ (} s \times 1 \text{)}$$

- Embodies *hypothesized mechanisms* through *model parameters* θ
- θ includes cell and virus production, death, clearance rates; treatment efficacy parameters; etc
- θ dictates *pattern of progression* over time (*deterministic*) under any *treatment pattern* $u(t)$

Control theory: Mathematical theory and techniques for modifying (*controlling*) the behavior of such systems

- *Goal* – Optimize some *objective function*, e.g., drive viral load *set point* below a threshold while keeping “*cost of therapy*” low
- I.e., determine $u(t)$ to achieve this objective

HIV dynamic models and control

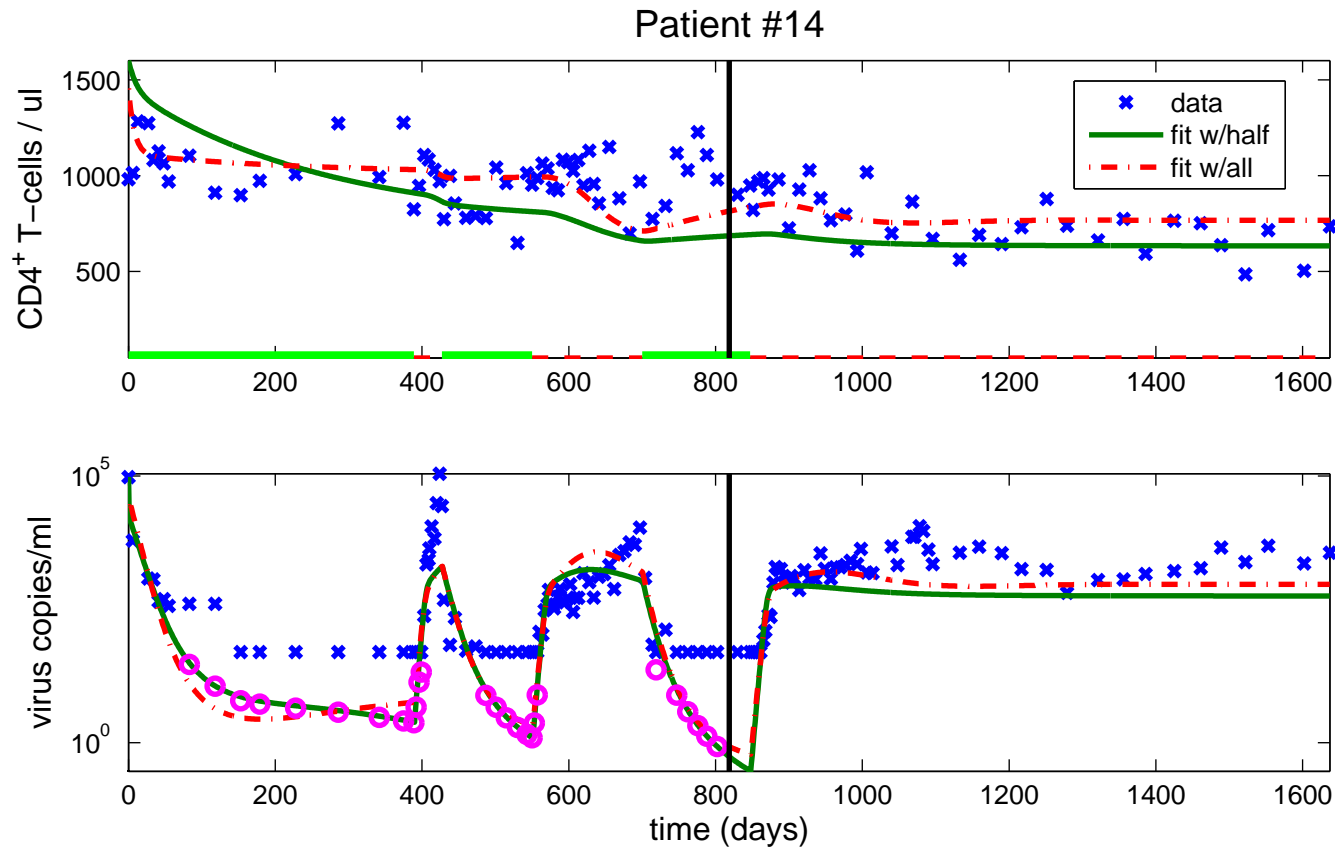
Our ultimate goal: Use *HIV dynamic models* and *control* along with *simulation* to *design treatment strategies* $u(t)$ for acute HIV infection and to *design clinical trials* to study them

- Find strategies that “*do well*” for individuals and for the population
- Need *evidence* supporting HIV dynamic model \implies *data* (e.g., *measured* CD4, VL, other stuff *over time* on lots of subjects)
- *Intra-subject variation* due to assay error, realization error; *left-censoring* of viral loads due to assay *lower limits of quantification*
- Substantial *inter-subject variation* \iff heterogeneity in mechanisms θ across the subject population

For both fitting to data and simulation: Must *embed* the (*deterministic*) mathematical model in a *statistical framework* that characterizes faithfully *inter-* and *intra-subject variation*

HIV dynamic models and control

Data: Eric has been collecting intensive *longitudinal* viral loads, CD4 counts on a *cohort* of ≥ 150 acutely-infected subjects for > 7 years



Mathematical-statistical framework

Mathematical model: $\dot{x}(t, \theta) = g\{t, x(t, \theta), \theta\}$, solution $x(t, \theta)$ ($s \times 1$)

- Observations *not available* on all s states
- $\bar{x} = \mathcal{O}x$ for *observation operator* \mathcal{O}
- E.g., CD4 and VL only

Statistical framework: Embed \bar{x} in a *hierarchical statistical model*

- For each subject i in the population, conceive of a *bivariate* (CD4, VL) *subject-specific stochastic process* under $u(t)$

$$Y_i\{t, u(t)\} = [Y_i^{CD4}\{t, u(t)\}, Y_i^{VL}\{t, u(t)\}]^T$$

- Depends on treatment strategy $u(t)$ up through time t

Mathematical-statistical framework

Intra-subject model: Decompose into

$$Y_i\{t, u(t)\} = \bar{x}\{t, u(t), \theta_i\} + e_i\{t, u(t)\}$$

- $e_i\{t, u(t)\}$ is the *deviation process* – *realizations*, *assay errors*
- $e_i\{t, u(t)\}$ *average out to zero* over *all possible realizations*, *assay errors* (conditional on θ_i and the strategy imposed)
- Interpret $\bar{x}\{t, u(t), \theta_i\}$ as *average* trajectories over *all possible realizations* we could see on subject i under strategy $u(t)$
- *Also*, assumptions on (conditional) *correlation* (across t and among elements of $e_i\{t, u(t)\}$), *variances*, *probability distribution*

Inter-subject model: θ_i is an “*inherent characteristic*” of subject i

- *Probability distribution* $p(\theta_i; \theta^*, D)$, e.g., $\theta_i \sim \mathcal{N}(\theta^*, D)$
- Could also be conditional on *subject characteristics*

Mathematical-statistical framework

Result: Full description of the hypothesized *data-generation process* in *continuous time*

- For *individual* subjects (randomly-chosen from the *population*)
- And thus for *samples of such subjects* drawn at random from the population
- For *large enough* sample \implies effectively, knowledge of the *entire population*
- Basis for *simulation* of “*virtual*” subjects

Needed: Full characterization based on *data*

Mathematical-statistical framework

Data: For subject i , $i = 1, \dots, N$, observed at n_i times t_{i1}, \dots, t_{in_i}

- $U_i(t)$ = actual *ART pattern* over entire observation period (*known*)
- $Y_{ij} = (Y_{ij}^{CD4}, Y_{ij}^{VL})^T$ at time $t_{ij} \implies Y_i = (Y_{i1}, \dots, Y_{in_i})^T$
- Conceive $Y_{ij} = Y_i\{t_{ij}, U_i(t_{ij})\}$ (similarly for e_i)
- *Eric's data* – $N \approx 150$, $n_i \approx 30\text{--}60$
- A_i = possible *subject characteristics*

Nonlinear mixed model (bivariate response): *Fit* to data

$$Y_{ij} = \bar{x}\{t_{ij}, U_i(t_{ij}), \theta_i\} + e_{ij}, \quad j = 1, \dots, n_i$$

$$\theta_i \sim p(\theta_i; \theta^*, D), \quad i = 1, \dots, N$$

Mathematical-statistical framework

Challenges:

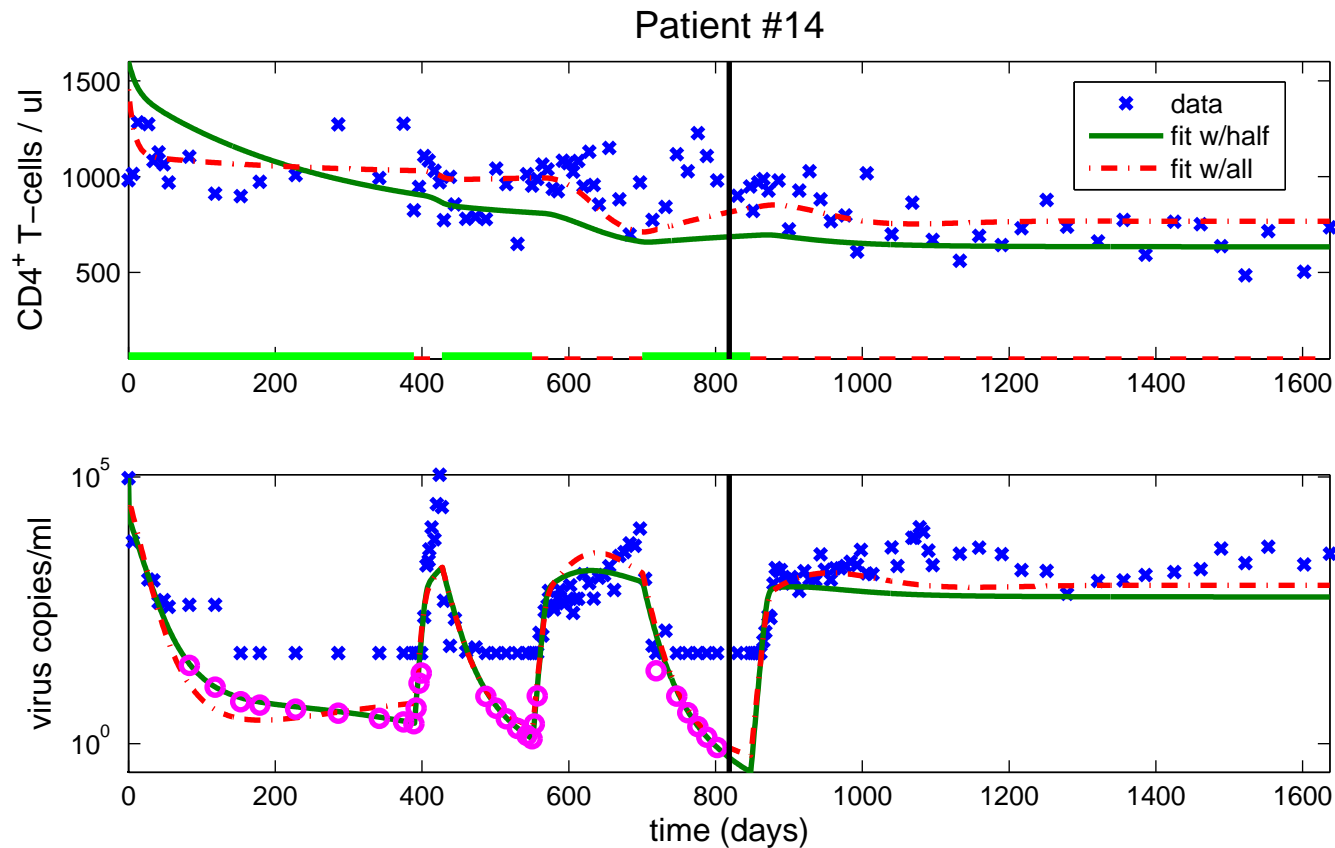
- *Left-censoring* of VL by *lower assay limit*
- $\dim(\theta) > 25$ and not all *identifiable* from CD4, VL only
- Components of \bar{x} only calculable *numerically* by *forward solution* of ODEs

Two-stage approach:

- For each i , estimate θ_i via EM algorithm to handle censoring incorporating *regularization* to address *identifiability/dimensionality*
- Use resulting $\hat{\theta}_i$ as “data” to obtain $\hat{\theta}^*$, \hat{D} using moment methods

Mathematical-statistical framework

Predictive capability:



Mathematical-statistical framework

Simulation:

- Generate N_{sim} “*virtual subjects*” by generating θ_i^* , $i = 1, \dots, N_{sim}$, from $p(\theta_i; \hat{\theta}_*, \hat{D})$
- Generate “*inherent trajectories*” $x\{t, u(t), \theta_i^*\}$ under a given $u(t)$ (continuous time)
- Add within-subject *deviations* according to *intra-subject* model to obtain “*virtual data*”
- Suitable $p(\theta_i; \hat{\theta}_*, \hat{D})$ determined by comparing “*virtual profile*” distributions (VL, CD4) to those from Multicenter AIDS Cohort Study (MACS, $u(t) \equiv 0$) and Eric’s data (various $u(t)$)
- Mixture of normals

Design of a clinical trial

Armed with this framework: Use to *design treatment strategies* and *clinical trials*

Our first step: *Proof of principle* – can we use this capability to assist in addressing a question involving *non-adaptive treatment strategies*?

- *Unresolved* – Whether or not individuals *acutely-infected* with HIV should be treated with ART
- *More precisely* – Is it better to give ART for *some period* following acute infection (“*train*” the immune system, “*self-vaccinate*”) or is it better to give no treatment at all until later (delay *drug resistance*, etc)
- *Primary endpoint* – VL *set point* at 12 months

Design of a clinical trial

Which strategies to study? $u(t) \equiv 0$ vs. strategies of the form

$$\begin{aligned}u(t) &= 1, 0 \leq t \leq \tau \\ &= 0, t > \tau\end{aligned}$$

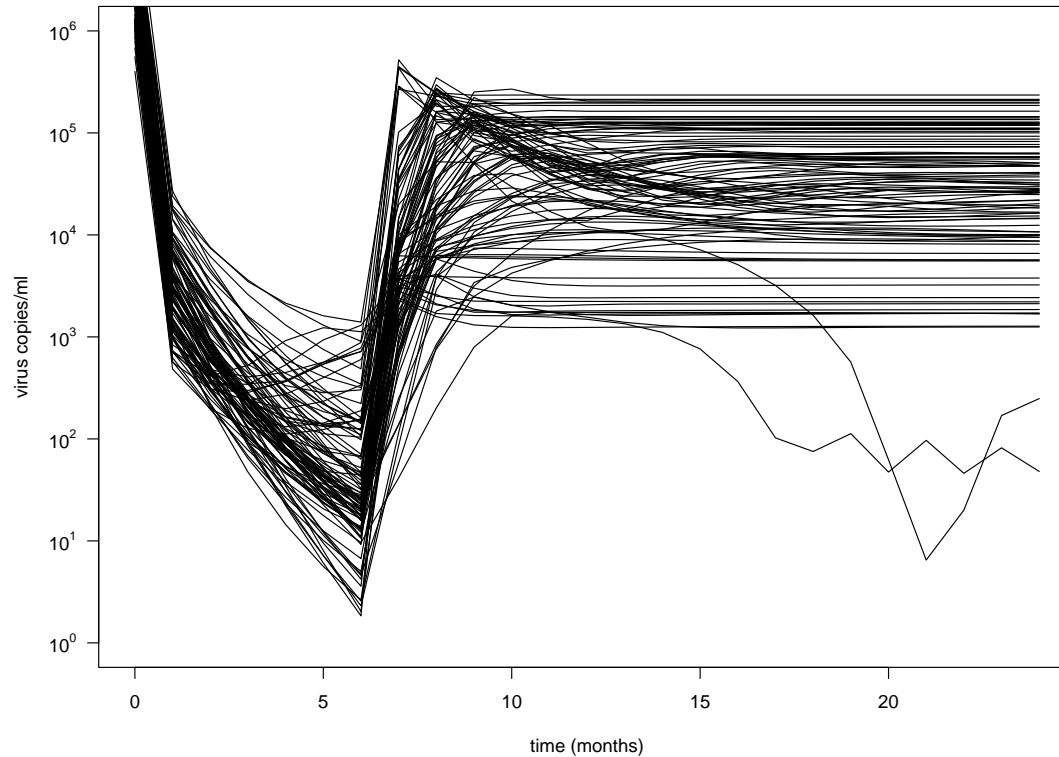
for *termination times* $\tau = 3, 4, \dots, 12$ months

Approach: Evaluate effects of candidate strategies on the (*virtual*) *population* by *simulation*

- Insight into which strategies to study based on their anticipated effects on the entire *population*

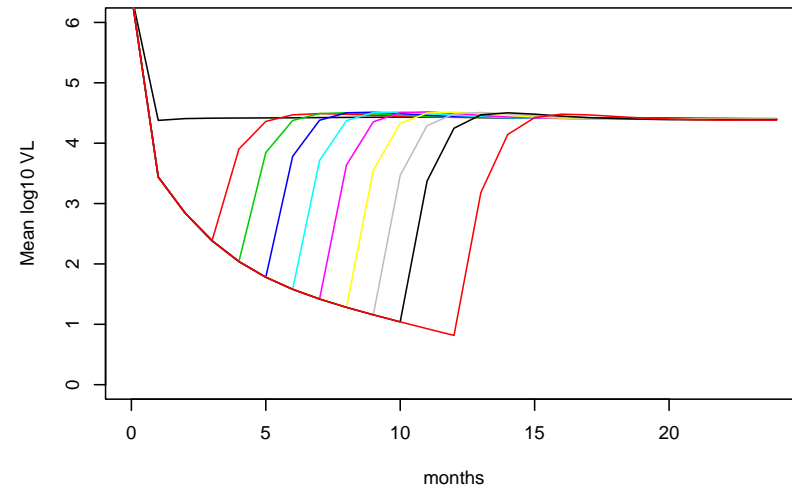
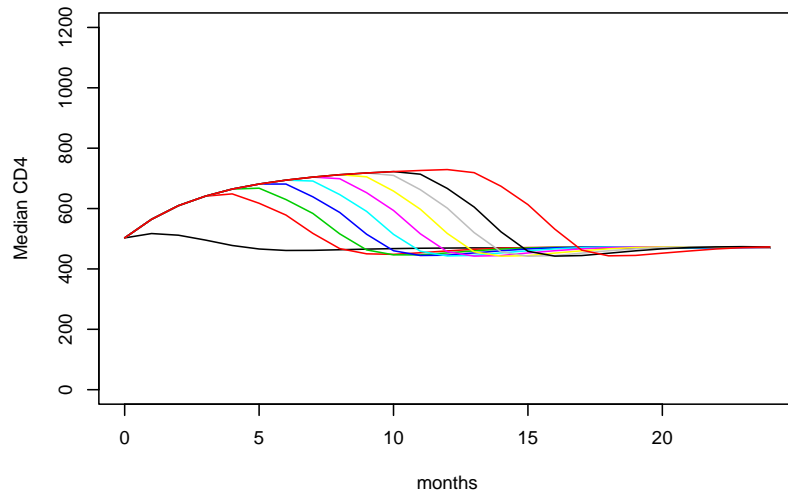
Design of a clinical trial

Strategy $u(t)$ with $\tau = 6$: 100 “*virtual*” “*inherent*” viral load trajectories with ART *terminated at 6 months*, i.e., $u(t) = 1, 0 \leq t \leq 6$, $u(t) = 0, t > 6$



Design of a clinical trial

Different termination times τ : Means of 15,000 “*virtual*” CD4 and viral load data profiles with $u(t) = 1, 0 \leq t \leq \tau, u(t) = 0, t > \tau,$
 $\tau = 0, 3, 4, \dots, 12$ months



Design of a clinical trial

Summary:

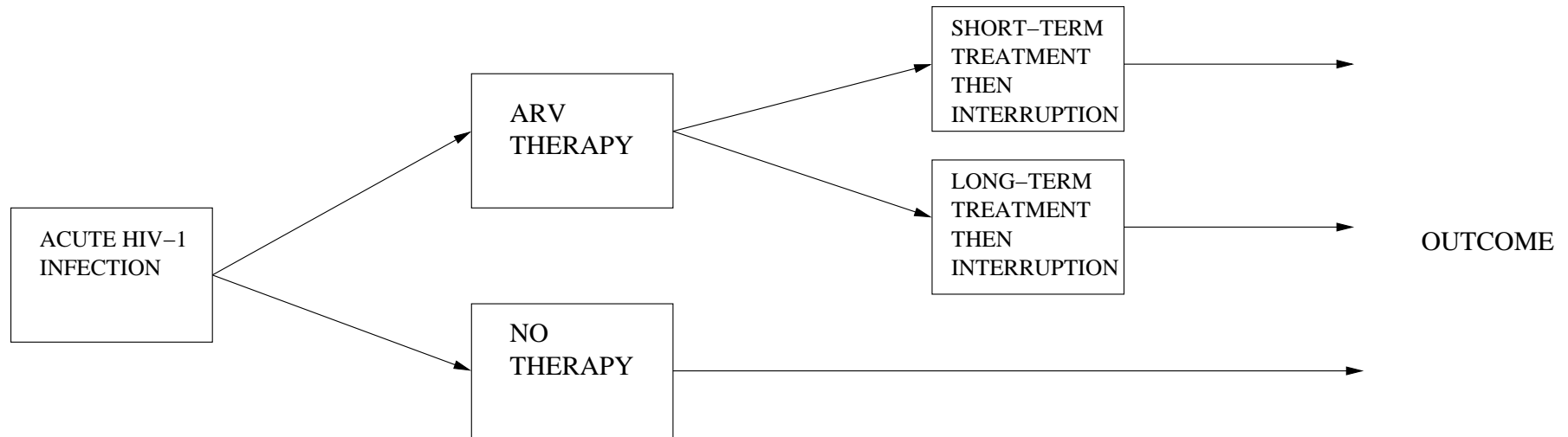
- Based on this (simple) HIV dynamic model, *no differences expected*
- Simple model does not represent adequately the *immune response*
- Simulations with a *refined model* showed larger *subpopulations* with *lowered VL set point* for larger τ ...
- ...but are less reliable (very little data on immune response)

Result: Study ART under *more than one termination time*

- $\tau = 3$ (“*short-term*”) and $\tau = 8$ months (“*long-term*”)

Design of a clinical trial

Trial schema: 1/2 pts randomized to ART, 1/2 pts to no ART



Design of a clinical trial

Plan: 3 year accrual period (36 patients), 1 year follow-up

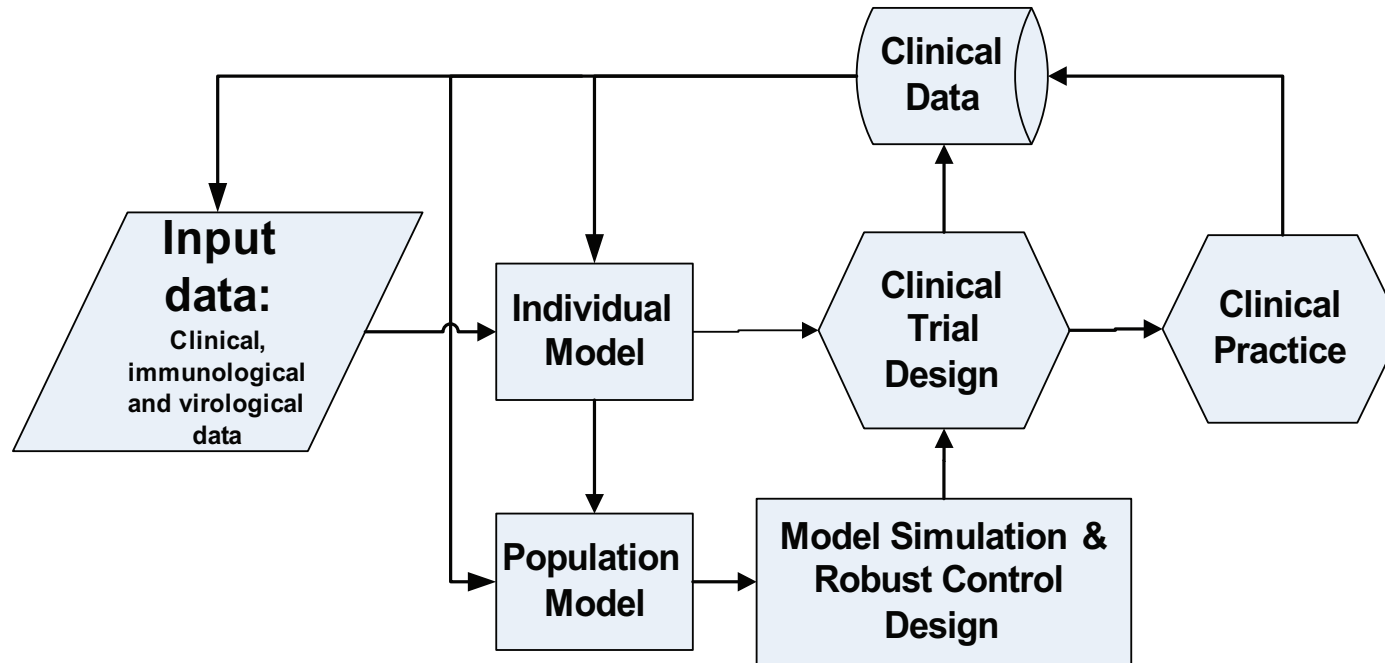
- Standard design considerations for primary VL comparison at 12 months
- *Intensive visit schedule* – collect CD4, VL, CTLs, viral fitness, etc
- Data collection more frequent when dynamics are anticipated to *be changing* (e.g., in the weeks *after ART termination*)

Design of STI strategies

Next step: Armed with *more informative data* (e.g., measurements reflecting aspects of *immune response*)

- Develop and validate *more realistic HIV dynamic models* . . .
- . . . and refine the entire *mathematical-statistical framework*
- . . . and use to develop and evaluate (“*virtually*”) potential *adaptive treatment strategies*
- *Receding horizon control* methods
- And design the *next trial* to study the most promising strategies . . .

Design of STI strategies



Closing remarks

- *Modeling and simulation* have a significant role to play in design of HIV treatment strategies
- *In principle* – could link dynamic models with models for PK, etc
- We envision cycles of smaller “*learning trials*” that provide richer information needed to develop more *refined adaptive strategies* that will then be evaluated in confirmatory trials
- We’ll see how this turns out!

Slides at: <http://www.stat.ncsu.edu/~davidian>

References

Adams, B.M., Banks, H.T., Davidian, M., and Rosenberg, E.S. (2007) Model fitting and prediction with HIV treatment interruption data. *Bulletin of Mathematical Biology* **69**, 563–584.

Rosenberg, E.S., Davidian, M., and Banks, H.T. (2007) Using mathematical modeling and control to develop structured treatment interruption strategies for HIV infection. *Drug and Alcohol Dependence* special supplement issue on “Customizing Treatment to the Patient: Adaptive Treatment Strategies” **88S**, S41-S51.