

**ASSESSMENT OF DRUGS EFFECTS
IN AIDS PATIENTS TREATED
BY HAART BY STATE SPACE MODELS**

By

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- Introduction to treatment of HIV-infected individuals by anti-retroviral drugs. (HAART and STI).
- The data, the State space model and Advantages. A State Space Model for HIV Pathogenesis Under Anti-viral Drugs.
- A Stochastic Model of HIV Pathogenesis Under HAART and Anti-viral drugs; Stochastic Differential Equations.
- A Statistical Model of HIV Pathogenesis Under HAART and Anti-viral drugs Based on RNA HIV Copies per ml of Blood Over time.
- A State Space Model for HIV Pathogenesis under Treatment.
- Estimation of Parameters Using State Space Models and Multi-level Gibbs Sampling Method.
- An Illustrative Example.
- Conclusions.

Introduction

1. Highly Active Anti-retroviral Therapy (HAART)

- Recent treatment protocol
- Combination of three drugs: 2 NRTIs plus 1 PI or 1 NNRTI.
 - Nucleoside Reverse Transcriptase Inhibitor (NRTI), e.g. Zidovudine, Stavudine, Lamivudine.
 - Protease Inhibitor (PI), e.g. Ritonavir, Indinavir, Nelfinavir
 - Non-nucleoside Reverse Transcriptase Inhibitor (NNRTI), e.g. Efavirenz

2. Recent studies on HAART

- Effective in suppression HIV replication
- Imperfect
 - Discontinuing HAART resulted in the return of HIV within 3-14 days
 - Clonal frequencies of CD4⁽⁺⁾ T and CD8⁽⁺⁾ T cells are reduced in those with sustained suppression of HIV virus

- New protocol, Structural Therapy Interruption by (STI), On-off of HAART Cycles. 7 days on/7 days off, 30 days on/ variable days off, etc.

3. Life-long treatment is required.

To evaluate new treatment protocols involving HAART (e.g. STI), to monitor the HIV progression under treatment by anti-viral drugs, to alert for possible development of drug resistance, and to provide guidance for developing optimal protocol involving HAART, one needs:

- to estimate the relative effects of NRTIs, NNRTIs and PIs
- to estimate the numbers of infectious HIV virus and non-Infectious HIV virus over Time

4. Methods non-existent to estimate effects of drugs (NRTIs, NNRTIs and PIs)

- We will develop state space models. We will use the model to develop efficient methods to estimate unknown parameters and state variables.
- This objective is achieved through the combination of state space model with the multi-level Gibbs sampling method

Table 2. The History of Drug Treatment

Days Partition	Drug Treatment	Inhibitor
[0, 49)	Zidovudine	NRTI
[49, 91)	No Drugs	No Inhibitor
[91, 98)	Ritonavir	PR Inhibitor
[98, 122)	Ritonavir, Lamivudine Zidovudine	NRTIs + PI
[122, 414)	Ritonavir, Lamivudine, Zidovudine Trimethoprim-sulfamethoxazole	NRTIs + PI
[414, 668)	Nelfinavir, Lamivudine, Zidovudine Trimethoprim-sulfamethoxazole	NRTIs + PI
[668, 773)	Nelfinavir, Lamivudine, Zidovudine	NRTIs + PI
[773, 1100)	Didanosine, Efavirenz, Stavudine	NRTIs + NNRTI

Data Set

- Longitudinal data over time from a single individual.
- Different drugs or drug combinations are used over different treatment periods.
- Treatment period is very long (over 3 years).
- Even under HAART, the total number of HIV copies may be very high (over 10,000/*ml* of blood).

The total number of HIV copies is the sum of infectious HIV and non-infectious HIV. Treatment is effective if the number of infectious HIV is small although the total number may be very high.

Some Models and Motivations

1. HIV Pathogenesis - - - a dynamic process involving interactions between different cells and HIV.

Under treatment, the basic state variables are:

- $T_P(t)$ = Number of productively HIV-infected CD4 T cells at time t ;
- $V_i(t)$ = Number of non-infectious ($i=0$) HIV and infectious HIV ($i=1$) at time t per ml of blood.

Some Models and Motivations (Continues)

2. Deterministic Dynamic Model

- The Perelson et al. Model.(Science 1996)

$$\frac{d}{dt}T_p(t) = ck_T(1 - \xi_R)V_1(t) - \mu_T T_P(t), \quad (1)$$

$$\frac{d}{dt}V_0(t) = \xi_P N T_P(t) \mu_T - \mu_V V_0(t), \quad (2)$$

$$\frac{d}{dt}V_1(t) = (1 - \xi_P) N T_P(t) \mu_T - (\mu_V + k_T) V_1(t), \quad (3)$$

where $k_T = kT$, k =HIV infection rate of T cells by HIV, $T(t) = T$ = Number of total uninfected CD4 T cells (assumed independent of time t); c =proportion of activated uninfected CD4 T cells; N = Total number of HIV generated by the death of each T_P cells; $\{\mu_T, \mu_V\}$ = death rate of T_P cells and HIV respectively; ξ_R =Probability that RNA HIV \rightarrow DNA HIV is blocked by NRTIs or NNRTIs; ξ_P =Probability that a newly generated HIV becomes non- infectious by the inhibition of protease by PIs or by the damage of reverse transcriptase by NRTIs or NNRTIs during activation and division of productively infected CD4 T cells.

Some Models and Motivations (Continues)

- Assumptions in the Perelson Model

(a) The total number of uninfected CD4 T cells ($T(t) = T$) is assumed a constant independent of time t .

(b) All parameters $\{k, \mu_T, \mu_V, \xi_R, \xi_P, N, c\}$ are constants independent of time t . (Time homogeneous).

(c) Latently HIV-infected CD4 T cells are ignored because its contribution to the production of HIV is very small.

Assumptions (a)-(b) are valid only if the treatment period is very small. If the treatment period is long and if different drugs are used over different time periods, (a)-(b) can not be assumed.

The model is deterministic in that all randomness are ignored.

- Some serious problems in the Perelson Model

- The parameters are not identifiable, e.g. the effects of NRTI, NNRTIs and PI drugs are mixed with other unknown parameters in the model and can not be estimated.
- When the treatment period is long and when different drugs

have been used over different time periods, the above assumptions (a)-(b) can not be satisfied so the model is not applicable.

- Deterministic model has ignored randomness of many variables.

Some Models and Motivations (Continues)

3. The Stochastic Model

- Extend the above model into stochastic model. e.g. $\{T_P(t), V_0(t), V_1(t)\}$ are stochastic processes.
- Partition the treatment period into an union of non-overlapping sub-intervals each with a short period and within each sub- interval, the same drug or drug combination is used.
- Assume a time-homogeneous stochastic model in each sub- interval.

This stochastic model can be presented by the following stochastic differential equations. (We will illustrate the derivation latter on.)

$$\frac{d}{dt}T_P(t) = c(t)k_T(t)(1 - \xi_R(t))V_1(t) - \mu_T T_P(t) + \epsilon_T(t), \quad (4)$$

$$\frac{d}{dt}V_0(t) = \xi_P(t)NT_P(t)\mu_T - \mu_V V_0(t) + \epsilon_0(t), \quad (5)$$

$$\frac{d}{dt}V_1(t) = (1 - \xi_P(t))NT_P(t)\mu_T - (\mu_V + k_T(t))V_1(t) + \epsilon_1(t), \quad (6)$$

where $\{c(t) = c_i, k_T(t) = k(t)T(t) = k_T(i), \xi_R(t) = \xi_R(i), \xi_P(t) = \xi_P(i)\}$ for all $t \in L_i$, the i -th treatment period and where $\{\epsilon_T(t), \epsilon_i(t), i = 0, 1\}$ are the random noises derived by subtracting the conditional mean numbers from the corresponding random variables respectively.

Some Models and Motivations (Continues)

4. Statistical Model

Wu et al(Stat. Medicine 1998) have proposed a statistical model to assess effects of drugs in AIDS patients treated with antiviral drugs.

The statistical model is

$$y_j = f(\Theta) + e_j, j = 1, \dots, n,$$

where y_j is the observed number of RNA virus copies at time t_j , Θ the totality of all parameters and e_j a measurement error which is assumed as a normal variable and where $f(\Theta)$ is a deterministic (non-random) function derived by solving the system of differential equations from the Perelson et al. model(1996, Science).

- Some Serious Problems in the Statistical Model
 - Suffer the same serious drawbacks as in the Perelson Deterministic model. (1) The parameters are not identifiable, e.g. the effects of NRTI, NNRTIs and PI drugs. (2) Assumptions (a)-(b) not satisfied. (3) Ignore randomness in the HIV pathogenesis.
 - If one partition the time into union of sub-intervals and assume a homogeneous model in each sub-interval. Then there are a

large number of parameters far beyond the data sets. It is not possible to use a few observations to estimate a large number of parameters by using the statistical model only without any prior information about the parameters

5. State Space Model= Stochastic Model + Statistic Model

- Dynamic process summarized in stochastic system model
- Information from data summarized in the Statistic Model
- Because of additional information from the stochastic system model, possible to estimate the state variables and a large number of parameters

State Space Model

1. Consists of Two Sub-models.

- Stochastic system model— a stochastic model describing the system through stochastic state variables; generate stochastic differential equations for the state variables; provide probability distributions for these variables.
- Observation model - - - a statistical model relating observed data of the system to the stochastic system
- Link information from these two models by multi-level Gibbs sampling procedure.

2. Advantages

- Identifiability problems solved because of additional information from stochastic model
- Model updated by new data available in the future through optimal procedure
- Estimating simultaneously the unknown parameters and the state variables

- Combining information from three sources: Information provided by the mechanism of the system; information provided by observed data; and information from previous experiences leading to Generalized Bayesian method

A Stochastic Model for HIV Pathogenesis under Protocols including HAART

1. State Variables

- Natural state variables:
 - $V_0(t)$: number of non-infectious HIV
 - $V_1(t)$: number of infectious HIV
 - $T_P(t)$: number of productively HIV-infected CD4⁽⁺⁾ T cells
- Augmented state variables:
 - $D_P(t)$: number of deaths of T_P cells during $[t, t + \Delta t)$
 - $D_{V_i}(t)$: number of free V_i HIV losing infectivity, dying, or removed
 - $F(t)$: number of V_1 HIV lost through infection of CD4⁽⁺⁾ T cells during $[t, t + \Delta t)$
 - $F_1(t)$: number of productively HIV-infected CD4⁽⁺⁾ T cells generated by the infection of actively dividing CD4⁽⁺⁾ T cells by free HIV during $[t, t + \Delta t)$
 - $R_j(t)$: number of non-infectious free HIV generated by the death of the j-th T_P cell under treatment by PI inhibitors

and/or NRTIs or NNRTIs.

- Build stochastic processes for the state variables to describe how the responses of the biological system evolve with time under the biological mechanisms and treatment stochastically.
- Identify probability distributions for these variables and hence the probability law for the HIV pathogenesis under treatment.

2. The important unknown parameters are:

- $\xi_R(t)$: probability of RNA HIV \rightarrow DNA HIV process blocked by the NRTI or NNRTI inhibitors
- $\xi_P(t)$: probability of a free non-infectious HIV released by the death of a productively infected T cell under treatment by PIs and/or NRTIs or NNRTIs
- $k_T(t) = kT(t)$, k = infection rate of activated CD4 T cells.
- $c(t)$ = The proportion of activated cells among the uninfected CD4 T cells
- Death rates (μ_T, μ_V) of T_P cells and HIV respectively
- N = The number of HIV generated by the death of each T_P cell

We will estimate the above parameters by combining the state space model with the multi-level Gibbs sampling method. The parameters $\{\xi_R(t), \xi_P(t), k_T(t), c(t)\}$ are time dependent. The parameters $\{\mu_T, \mu_V, N\}$ are time independent.

3. Stochastic Model and Stochastic Equations

Consider the time interval $[t, t + \Delta t)$. Then $\{T_P(t + \Delta t), V_0(t + \Delta t), V_1(t + \Delta t)\}$ derive from $\{T_P(t), V_0(t), V_1(t)\}$ through stochastic transitions. These stochastic transitions are characterized by the above augmented state variables $\{F(t), F_1(t), D_P(t), D_{V_0}(t), D_{V_1}(t), R_j(t), j = 1, \dots, D_P(t)\}$.

$$T_P(t + \Delta t) = T_P(t) + F_1(t) - D_P(t), \quad (7)$$

$$V_0(t + \Delta t) = V_0(t) + \sum_{j=1}^{D_P(t)} R_j(t) - D_{V_0}(t) = R(t) - D_{V_0}(t), \quad (8)$$

$$V_1(t + \Delta t) = V_1(t) + \sum_{j=1}^{D_P(t)} [N(t) - R_j(t)] - F(t) - D_{V_1}(t), \quad (9)$$

4. Probability Distribution of Augmented State Variables

- $[F(t), D_{V_1}(t)] \mid V_1(t) \sim \text{Multinomial}[V_1(t); k_T(t)\Delta t, \mu_{V_1}(t)\Delta t]$;
- $F_1(t) \mid F(t) \sim \text{Binomial}\{[c(t)F(t)]; [1 - \xi_R(t)]\}$, where $[c(t)F(t)]$ is the largest integer $\leq c(t)F(t)$;

- $D_P(t) \mid T_P(t) \sim \text{Binomial} [T_P(t); \mu_T(t)\Delta t]$;
- $\{R_j(t), j = 1, \dots, D_P(t)\} \mid D_P(t) > 0 \sim \text{Binomial} [N(t); \xi_P(t)]$
independently ($R_j(t) = 0$ if $D_P(t) = 0$.);
- $D_{V_0}(t) \mid V_0(t) \sim \text{Binomial} [V_0(t); \mu_{V_0}(t)\Delta t]$.

5. Stochastic Differential Equations for $\{T_P(t), V_j(t), j = 0, 1\}$ respectively

$$dT_P(t) = T_P(t + \Delta t) - T_P(t) = F_1(t) - D_P(t) = \{c(t)k_T(t)[1 - \xi_R(t)]V_1(t) - T_P(t)\mu_T(t)\}\Delta t + \varepsilon_1(t)\Delta t, \quad (10)$$

$$dV_0(t) = V_0(t + \Delta t) - V_0(t) = \sum_{j=1}^{D_P(t)} R_j(t) - D_{V_0}(t) = R(t) - D_{V_0}(t) = \{N(t)\xi_P(t)T_P(t)\mu_T(t) - \mu_{V_0}(t)V_0(t)\}\Delta t + \varepsilon_2(t)\Delta t, \quad (11)$$

$$dV_1(t) = V_1(t + \Delta t) - V_1(t) = \sum_{j=1}^{D_P(t)} [N(t) - R_j(t)] - F(t) - D_{V_1}(t) = \{N(t)[1 - \xi_P(t)]\mu_T(t)T_P(t) - k_T(t)V_1(t) - \mu_{V_1}(t)V_1(t)\}\Delta t + \varepsilon_3(t)\Delta t, \quad (12)$$

A State Space Model for HIV Pathogenesis under Protocols including HAART

The stochastic system model of this state space model is given by the stochastic model given above through stochastic differential equations. The observation model is a statistic model based on the observed number of RNA HIV copies per ml of blood over time.

1. The Stochastic System Model and the Probability Distribution of State Variables

- Θ : collection of all parameters.

- Letting $\Delta t \sim 1$ corresponding to a small interval such as 0.1 day.

Then the state variables are $\mathbf{X} = \{\underline{X}(t), t = 0, 1, \dots, t_M\}$, where

$$\underline{X}(t) = \{T_P(t), V_j(t), j = 0, 1\}$$

- For implementing the multi-level Gibbs sampling method, define the Unobservabled state variables $\mathbf{U} = \{\underline{U}(t), t = 0, 1, \dots, t_M\}$, where $\underline{U}(t) = \{F(t), D_P(t), R(t)\}$

The conditional density of $\underline{U}(t)$ given $\underline{X}(t)$ is

$$\begin{aligned}
P\{\underline{U}(t)|\underline{X}(t)\} &= C_1(t)[\mu_T(t)]^{D_P(t)}[1 - \mu_T(t)]^{T_P(t)-D_P(t)} \\
&\times [k_T(t)]^{F(t)}[1 - k_T(t)]^{V_1(t)-F(t)} \\
&\times [\xi_P(t)]^{R(t)}[1 - \xi_R(t)]^{D_P(t)N-R(t)}, \quad (13)
\end{aligned}$$

where $C_1(t) = \binom{V_1(t)}{F(t)} \binom{T_P(t)}{D_P(t)} \binom{ND_P(t)}{R(t)}$ and $R(t) = 0$ if $D_P(t) = 0$.

The conditional density of $\underline{X}(t+1)$ given $\{\underline{U}(t), \underline{X}(t)\}$ is

$$\begin{aligned}
P\{\underline{X}(t+1)|\underline{U}(t), \underline{X}(t)\} &= \binom{[c(t)F(t)]}{A_1(t)} [\xi_R(t)]^{A_2(t)} [1 - \xi_R(t)]^{A_1(t)} \\
&\times \binom{V_0(t)}{B_1(t)} [\mu_{V_0}(t)]^{B_1(t)} [1 - \mu_{V_0}(t)]^{V_0(t)-B_1(t)} \\
&\times \binom{V_1(t) - F(t)}{B_2(t)} \left[\frac{\mu_{V_1}(t)}{1 - k_T(t)} \right]^{B_2(t)} \\
&\times \left[1 - \frac{\mu_{V_1}(t)}{1 - k_T(t)} \right]^{V_1(t)-F(t)-B_2(t)}, \quad (14)
\end{aligned}$$

where $\{A_1(t) = T_P(t+1) - T_P(t) + D_P(t), A_2(t) = [c(t)F(t)] - A_1(t)\}$ and $\{B_1(t) = V_0(t) - V_0(t+1) + R(t), B_2(t) = V_1(t) - V_1(t+1) + ND_P(t) - R(t) - F(t)\}$.

The joint density of $\{\mathbf{X}, \mathbf{U}\}$ given Θ is

$$\begin{aligned}
P\{\mathbf{X}, \mathbf{U}|\Theta\} &= P\{\underline{X}(0)|\Theta\} \prod_{t=1}^{t_M} P\{\underline{X}(t)|\underline{U}(t-1), \underline{X}(t-1)\} \\
&\times P\{\underline{U}(t-1)|\underline{X}(t-1)\}, \quad (15)
\end{aligned}$$

2. The Observation Model and the Probability Distribution of the Observed RNA Virus Copies

- y_j : observed total number of HIV RNA virus load
- $y_j = V(t_j) + e_j \sqrt{V(t_j)}, j = 1, \dots, n$
- $V(t_j) = V_0(t_j) + V_1(t_j)$ at time $t_j, j = 1, 2, \dots, n$
- $e_j = (y_j - V(t_j)) / \sqrt{V(t_j)}$
- e_j 's are independently distributed as normal variates with means 0 and variance σ^2

Let $\mathbf{Y} = \{y_j, j = 1, \dots, n\}$ and put:

$$f_Y\{y_j|X(t_j)\} = \{2\pi V(t_j)\sigma^2\}^{1/2} \exp\left\{-\frac{1}{2V(t_j)\sigma^2}[y_j - V(t_j)]^2\right\}. \quad (16)$$

Then the joint density of $\{\mathbf{X}, \mathbf{U}, \mathbf{Y}\}$ given Θ is:

$$\begin{aligned} P\{\mathbf{X}, \mathbf{U}, \mathbf{Y}|\Theta\} &= P\{\underline{X}(0)|\Theta\} \prod_{j=1}^n f_Y\{Y(j)|V(t_j)\} \\ &\times \prod_{t=t_{j-1}+1}^{t_j} P\{\underline{U}(t-1)|\underline{X}(t-1)\} \\ &\times P\{\underline{X}(t)|\underline{X}(t-1), \underline{U}(t-1)\}. \end{aligned} \quad (17)$$

Estimation of Unknown Parameters and State Variables

1. Unknown Parameters $\{c(t), N(t), \mu_T(t), \mu_{V_i}(t), i = 0, 1, k_T(t), \xi_R(t), \xi_P(t), \sigma^2\}$

- $\Theta_1 = \{c, N\}$
- $\Theta_2 = \{\mu_T, \mu_V, \sigma^2, \xi_R(t), \xi_P(t), k_T(t), t = 1, \dots, k\}$

2. Two Stage Procedure to Estimate these Parameters

- Step 1: Given Θ_2 and the observed data, use least square procedure to estimate $\Theta_1 = \{c, N\}$.
- Step 2: Given the observed data and with Θ_1 obtained from Step 1, use the multi-level Gibbs sampling procedure to estimate Θ_2 and the state variables such as the numbers of infectious HIV and non-infectious HIV over time.
- Step 3: With Θ_2 obtained from Step 2, go back to Step 1 and continue the process until convergence.

3. Multi-level Gibbs sampling procedure for estimating Θ_2 and the state variables given $\{\mathbf{Y}, \Theta_1\}$

- Combining a large sample from $P\{\mathbf{U}, \mathbf{X}|\Theta\}$ with $P\{\mathbf{Y}|\Theta, \mathbf{X}\}$ through the weighted Bootstrap method due to Smith and Gelfant [24], we generate $\{\mathbf{U}, \mathbf{X}\}$ (denote the generated sample $\{\mathbf{U}^{(*)}, \mathbf{X}^{(*)}\}$) from $P\{\mathbf{U}, \mathbf{X}|\Theta, \mathbf{Y}\}$ although the latter density is unknown.
- On substituting $\{\mathbf{U}^{(*)}, \mathbf{X}^{(*)}\}$ which are generated by the above step, we generate Θ_2 from the conditional density $P\{\Theta_2|\mathbf{X}^{(*)}, \mathbf{U}^{(*)}, \mathbf{Y}, \Theta_1\}$
- With Θ_2 being generated from Step 2 above, go back to Step 1 and repeat the above [1]-[2] loop until convergence.

Table 1. The Observed Numbers of HIV RNA Virus Load of an HIV Infected Patient

Days Since HIV Infection	RNA Copies/ml	Predicted RNA Copies/ml \pm Std Error	Predicted Infectious RNA Copies/ml \pm Std Error
80	150000	149104 \pm 58003	149104 \pm 58003
88	160000	167419 \pm 68292	167419 \pm 68292
92	210000	208541 \pm 170760	4659 \pm 4114
93	120000	116406 \pm 137000	2032 \pm 2490
95	110000	111653 \pm 7433	1931 \pm 1295
99	43000	43647 \pm 21277	9202 \pm 5024
120	1200	1364 \pm 2806	54 \pm 253
179	950	615 \pm 1461	92 \pm 313
204	\leq 400	532 \pm 1493	18 \pm 232
232	20000	20109 \pm 9440	1418 \pm 720
248	14000	14026 \pm 7412	743 \pm 398
260	36000	36286 \pm 17361	5037 \pm 2390
291	\leq 400	467 \pm 1272	39 \pm 269
331	\leq 400	551 \pm 1254	31 \pm 186
353	\leq 400	528 \pm 1455	19 \pm 164
437	34000	33805 \pm 18528	5068 \pm 2839
465	4400	4383 \pm 2672	332 \pm 214
527	\leq 400	517 \pm 1349	24 \pm 142
592	4100	3938 \pm 2807	575 \pm 370
671	12000	12088 \pm 6343	1110 \pm 618
746	3300	3389 \pm 2208	391 \pm 271
774	5700	5799 \pm 3098	854 \pm 483
802	\leq 400	487 \pm 1471	29 \pm 176
894	\leq 400	758 \pm 1591	56 \pm 185
984	1600	1897 \pm 1920	279 \pm 364
1073	1100	1354 \pm 1956	169 \pm 367

Table 3. The Estimate of Parameters

Periods Days after Infection	Estimate of $\{\xi_P(t)\}$ \pm Std Error	Estimate of $\{\xi_R(t)\}$ \pm Std Error	Estimate of $\{k_T(t)\}$ \pm Std Error
[0, 49)	0.01 \pm 6.0064E-04	0.845 \pm 4.1930E-03	2.85E-02 \pm 5.8051E-04
[49, 91)	0.0 \pm 0.0	0.0 \pm 1.1166E-02	5.101E-03 \pm 1.7281E-04
[91, 98)	0.9775 \pm 5.4589E-04	0.0 \pm 1.2851E-02	6.05E-02 \pm 9.6712E-04
[98, 102)	0.5 \pm 4.0100E-03	0.9998 \pm 1.2023E-03	6.67E-01 \pm 2.1950E-03
[102, 122)	0.865 \pm 0.3496	0.9885 \pm 0.3225	1.5E-01 \pm 6.8427E-02
[122, 188)	0.7535 \pm 0.3341	0.9975 \pm 0.3901	5.8152E-02 \pm 2.7205E-02
[188, 226)	0.806 \pm 0.3573	0.9971 \pm 0.4263	1.985E-01 \pm 9.9543E-02
[226, 236)	0.915 \pm 0.4316	0.856 \pm 0.3164	2.15E-02 \pm 1.0879E-02
[236, 251)	0.935 \pm 0.4411	0.8985 \pm 0.3363	3.95E-02 \pm 2.0148E-02
[251, 284)	0.8245 \pm 0.3886	0.81 \pm 0.2907	8.652E-02 \pm 4.2733E-02
[284, 311)	0.7505 \pm 0.3539	0.9975 \pm 0.4543	1.251E-01 \pm 6.2958E-02
[311, 337)	0.81 \pm 0.4041	0.9975 \pm 0.4820	1.51E-01 \pm 8.3933E-02

Table 3 The Estimate of Parameters (Continued)

Periods Days after Infection	Estimate of $\{\xi_P(t)\}$ \pm Std Error	Estimate of $\{\xi_R(t)\}$ \pm Std Error	Estimate of $\{k_T(t)\}$ \pm Std Error
[337, 414)	0.845 ± 0.4266	0.997 ± 0.4831	1.935E-01 ± 0.1101
[414, 444)	0.8085 ± 0.4084	0.8112 ± 0.3092	7.7E-02 $\pm 4.1171E-02$
[444, 465)	0.9 ± 0.4544	0.9975 ± 0.4857	5.7455E-02 $\pm 3.1137E-02$
[465, 528)	0.85 ± 0.4291	0.9973 ± 0.4847	1.9358E-01 ± 0.1098
[528, 668)	0.804 ± 0.4069	0.985 ± 0.4066	1.45E-01 $\pm 8.5151E-02$
[668, 679)	0.7945 ± 0.4015	0.956 ± 0.4375	0.395 ± 0.2017
[679, 773)	0.845 ± 0.4270	0.9865 ± 0.4698	8.5295E-02 $\pm 4.7300E-02$
[773, 786)	0.805 ± 0.4074	0.9785 ± 0.3630	7.286E-02 $\pm 4.3805E-02$
[786, 894)	0.845 ± 0.4270	0.997 ± 0.4836	1.756E-01 $\pm 9.9170E-02$
[894, 1100]	0.765 ± 0.3873	0.9885 ± 0.4679	7.55E-02 $\pm 4.2816E-02$

Conclusions

(a) The HAART involving two NRTI and one PI are very efficient to suppress HIV replication. At least one type of drugs is effective.

(b) The drug combination (Didanosine, lamivudine, efavirenz) of two NRTI drugs (Didanosine, lamivudine) and one NNRTI drug (efavirenz) appeared to be at least as good as the HAART involving two NRTI and one PI (AZT-3TC-Ritonavir, or AZT-3TC-Nelfinavir).

(c) To assess effects of drugs, using the total number of HIV is misleading and give wrong conclusions. The total number of HIV is very high (over 10,000/ml of blood), yet the number of infectious HIV/ml may be very low (less than 1000/ml), indicating that the drug combination is in fact very effective in suppressing HIV replication.

(d) Give some indication as to the time of development of drug resistance.

For example, during (300, 414) when the individual was treated by HAART involving two NRTIs (AZT,3TC) and one PI (Ritonavir), the

total number of infectious HIV fluctuates between 300/ml and 800/ml of blood during (300, 400), but at 400 days the number began to rise to 5000/ml and kept increasing until the PI (Ritonavir) were replaced by another PI (Nelfinavir) at day 414; then in 10 days the total number of infectious HIV dropped to very low level (around 500/ml) and stay at low level for a very long period. This indicates that some drug resistance to the drug Ritonavir had been developed by HIV at day 414.

(e) Interaction between the initial numbers of HIV and the selection of drug combination.

When the initial number of HIV is very high, the HAART with two NRTI and one PI appeared to be able to bring down the total number of infectious HIV from a very high level ($> 100,000/ml$ blood) to $\leq 500/ml$ in a few days; on the other hand, when the number of HIV infectious HIV is very low at the start, the combination of two NRTIs with a NNRTI such as efavirenz might better maintain suppression of HIV replication and for a longer period.

(f) It is more important to control HIV infection by NRTIs and/or NNRTI than by inhibition of protease in latter stages.

when the number of HIV has been brought down, it would be better to use the combination involving two NRTI with one NNRTI such as (Zidovudine,lamivudine, efavirenz).

(g) The importance of compliance.

For example, during (98, 122) when HAART involving (AZT-3TC-Ritonavir) was used, the number of infectious HIV may reach 5000/ml at some time points because of non-compliance due to side effects of the drugs; but when the drug Trimethoprin-sulfamethoxazole (not an AIDS drug) was added to HAART to alleviate side effects to maintain better compliance, the number of infectious HIV were kept very low all the times.

(h) Justification of the Use of Structural On and Off HAART Protocol

Clinical Implications

- Providing guidance for developing optimal treatment protocol
- Seeking optimal substitutes for drugs having high side effects, e.g.
Ritonavir and nelfinavir replaced by efavirenz
- Providing guidance for possible development of drug resistance
- Compare effects of different drugs