Viral Dynamics

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People living with HIV (2005)

TOTAL: 40.3 (36.7–45.3) million
Deaths resulting from HIV (2005)

TOTAL: 3.1 (2.8-3.6) million
New infections with HIV (2005)

TOTAL: 4.9 (4.3–6.6) million
Estimated Number of AIDS Cases and Deaths among Adults and Adolescents with AIDS, 1985–2003—United States

No. of cases and deaths (in thousands)

AIDS
Deaths

Year of diagnosis or death


1993 Case definition
Mathematics entered the field

Note. Adjusted for reporting delays.
What is HIV infection?

**The virus**

A retrovirus

Infects immune cells bearing:
CD4 & CCR5/ CXCR4

**The host**

CD4+ T-cells (or helper T cells)

Macrophages and dendritic cells
Typical Course of HIV Infection

No treatment

Drug Therapy

- Medical: a means of interfering with viral replication – treat or cure disease
- Mathematical: a means of perturbing a system and uncovering its dynamics
Model of HIV Infection

- Productively Infected Cell
- Death
- Clearance
- Infection Rate
- Virions/d
- Target Cell
Model of HIV Infection

\[
\frac{dT(t)}{dt} = \lambda - dT - kTV
\]
\[
\frac{dT^*(t)}{dt} = kTV - \delta T^*
\]
\[
\frac{dV(t)}{dt} = N\delta T^* - cV
\]

Variables

- \( T \): Target Cell Density
- \( T^* \): Infected Target Cell Density
- \( V \): Virus Concentration

Parameters

- \( \lambda \): Supply of target cells
- \( d \): Net loss rate of target cells
- \( k \): Infectivity rate constant
- \( \delta \): Infected cell death rate
- \( N\delta = p \): Virion production rate
- \( c \): Virion clearance rate constant

Initial Conditions

- \( T(0) = T_0 \)
- \( T^*(0) = 0 \)
- \( V(0) = V_0 \)
Model Used for Drug Perturbation Studies

\[
\frac{dT^*_I(t)}{dt} = (1 - \epsilon_{RT})kV_I T_0 - \delta T^*_I
\]

\[
\frac{dV_I(t)}{dt} = (1 - \epsilon_{PI})N\delta T^*_I - cV_I
\]

\[
\frac{dV_{NI}(t)}{dt} = \epsilon_{PI} N\delta T^*_I - cV_{NI}
\]

Drug efficacy

\(\epsilon_{RT}\quad \epsilon_{PI}\)

Subscripts:

“\(I\)”: infectious

“\(NI\)”: non-infectious

Solution of Model Equations Assuming 100% Efficacy of Protease Inhibitor Therapy; Target Cells Assumed Constant

\[ V(t) = V_0 \exp(-ct) + \frac{cV_0}{c-\delta} \left\{ \frac{c}{c-\delta} \left[ \exp(-\delta t) - \exp(-ct) \right] - \delta t \exp(-ct) \right\} \]

Solution has two parameters:
- \( c \) – clearance rate of virus
- \( \delta \) – death rate of infected cells
HIV-1: First Phase Kinetics

Perelson et al.
Science 271, 1582
1996
Productively infected CD4+ lymphocytes

$\tau_{1/2} < 1.5 \text{ d}$

HIV-1

$\tau_{1/2} < 30 \text{ min - 1 hr}$

10$^{10}$ to 10$^{12}$ virions/d from 10$^7$ to 10$^9$ T cells

Uninfected, activated CD4+ lymphocytes
Implications

- HIV infection is not a slow process
- Virus replicates rapidly and is cleared rapidly—can compute to maintain set point level > $10^{10}$ virions produced/day
- Cells infected by HIV are killed rapidly
- Rapid replication implies HIV can mutate and become drug resistant
## Rate of generation of HIV-1 mutants

<table>
<thead>
<tr>
<th>Base Changes</th>
<th>Probability of mutant</th>
<th>Number created/day</th>
<th>Number of possible mutants</th>
<th>Fraction of all possible mutants created/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0.74</td>
<td>$7.4 \times 10^7$</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>0.22</td>
<td>$2.2 \times 10^7$</td>
<td>$3.0 \times 10^4$</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>0.033</td>
<td>$3.3 \times 10^6$</td>
<td>$4.5 \times 10^8$</td>
<td>$7.4 \times 10^{-3}$</td>
</tr>
<tr>
<td>3</td>
<td>0.0033</td>
<td>$3.3 \times 10^5$</td>
<td>$4.5 \times 10^{12}$</td>
<td>$7.4 \times 10^{-8}$</td>
</tr>
</tbody>
</table>

Perelson, Essunger & Ho, AIDS 1997
Estimated Number of AIDS Cases and Deaths among Adults and Adolescents with AIDS, 1985–2003—United States

- AIDS
- Deaths

Year of diagnosis or death

Note. Adjusted for reporting delays.
HIV-1: Two Phase Kinetics

Combination Therapy

productively infected CD4+ lymphocytes

93-99%

$T_{1/2} \sim 1 \text{ d}$

HIV-1

1-7%

$T_{1/2} \sim 30 \text{ min}$

long-lived cell populations

$T_{1/2} \sim 14 \text{ d}$

uninfected, activated CD4+ lymphocytes
HIV-1: Two Phase Kinetics

Dynamics of HIV-1

- Productively infected CD4+ lymphocytes
  - $t_{1/2} \sim 1\, \text{d}$
- Uninfected, activated CD4+ lymphocytes
  - $t_{1/2} \sim 30\, \text{min}$
- Latently infected resting memory CD4+ lymphocytes
  - $t_{1/2}$ slow
- Long-lived cell populations
  - $t_{1/2} \sim 14\, \text{d}$

- HIV-1
  - 93-99%
  - 1-7%
Decay of latent reservoir on HAART

Finzi et al. Nat Med 1999

T? = 43.9 months
60.8 years to eradicate 10^5 cells
## Basic Biology of HIV-1 In Vivo Revealed by Modeling

<table>
<thead>
<tr>
<th></th>
<th>$t_{1/2}$</th>
<th>Contribution to viral load</th>
</tr>
</thead>
<tbody>
<tr>
<td>Virions:</td>
<td>&lt; 1 hr</td>
<td>$&gt;10^{10}$/day</td>
</tr>
<tr>
<td>Infected T cells:</td>
<td>0.7 d</td>
<td>93-99%</td>
</tr>
<tr>
<td>Infected long-lived cells:</td>
<td>14 d</td>
<td>1-7%</td>
</tr>
<tr>
<td>Latently infected T cells:</td>
<td>months - years</td>
<td>&lt; 1 %</td>
</tr>
</tbody>
</table>
Implications

- Due to long-lived infected cell populations, would need to treat HIV infected individuals for many years with 100% effective drugs to eradicate the virus. Initial estimates were 3-4 years of treatment, new estimates at least 10 years.
- But, do not have 100% effective therapy
What happens after the limit of detection is reached?

- **1st phase** ($t_{1/2} \sim$ days)
- **2nd phase** ($t_{1/2} \sim$ weeks)
- **3rd phase** ($t_{1/2} \sim$ months)?

HIV-1 RNA/ml vs. Treatment time
Pomerantz – supersensitive RT-PCR

How to explain low steady state?

For the standard model Bonhoeffer et al. JV 71:3275 1997 showed that there was a sensitive dependence of steady state VL on drug efficacy.
Two-Compartment Drug Sanctuary Model

\[
\begin{align*}
\dot{T}_1 &= \lambda_1 - d T_1 - (1 - \varepsilon)k V T_1 \\
\dot{T}_2 &= \lambda - d T_2 - (1 - f \varepsilon)k V T_2 \\
\dot{T}_1^* &= (1 - \alpha)(1 - \varepsilon)k V T_1 - \delta T_1^* \\
\dot{T}_2^* &= (1 - \alpha)(1 - f \varepsilon)k V T_2 - \delta T_2^* \\
\dot{C}_1^* &= \alpha(1 - \varepsilon)k V T_1 - \mu C_1^* \\
\dot{C}_2^* &= \alpha(1 - f \varepsilon)k V T_2 - \mu C_2^* \\
\dot{V}_1 &= N_T \delta T_1^* + N_C \mu C_1^* - c V_1 + D_1 (V_2 - V_1) \\
\dot{V}_2 &= N_T \delta T_2^* + N_C \mu C_2^* - c V_2 + D_2 (V_1 - V_2)
\end{align*}
\]
Drug sanctuary solves the problem

Two compartment model does not have sensitive dependence on $\varepsilon$
Part II

Hepatitis C Virus Modeling
<table>
<thead>
<tr>
<th>Source of virus</th>
<th>Type of Hepatitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>feces</td>
<td>A</td>
</tr>
<tr>
<td>blood/ blood-derived body fluids</td>
<td>B</td>
</tr>
<tr>
<td>blood/ blood-derived body fluids</td>
<td>C</td>
</tr>
<tr>
<td>blood/ blood-derived body fluids</td>
<td>D</td>
</tr>
<tr>
<td>feces</td>
<td>E</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Route of transmission</th>
<th>Type of Hepatitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>fecal-oral</td>
<td>A</td>
</tr>
<tr>
<td>percutaneous</td>
<td>B</td>
</tr>
<tr>
<td>permucosal</td>
<td>C</td>
</tr>
<tr>
<td>percutaneous</td>
<td>D</td>
</tr>
<tr>
<td>permucosal</td>
<td>E</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Chronic infection</th>
<th>Type of Hepatitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>no</td>
<td>A</td>
</tr>
<tr>
<td>yes</td>
<td>B</td>
</tr>
<tr>
<td>yes</td>
<td>C</td>
</tr>
<tr>
<td>yes</td>
<td>D</td>
</tr>
<tr>
<td>no</td>
<td>E</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Prevention</th>
<th>Type of Hepatitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>pre/post-exposure immunization</td>
<td>A</td>
</tr>
<tr>
<td>pre/post-exposure immunization</td>
<td>B</td>
</tr>
<tr>
<td>blood donor screening; risk behavior modification</td>
<td>C</td>
</tr>
<tr>
<td>pre/post-exposure immunization; risk behavior modification</td>
<td>D</td>
</tr>
<tr>
<td>ensure safe drinking water</td>
<td>E</td>
</tr>
</tbody>
</table>
## Estimates of Acute and Chronic Disease Burden for Viral Hepatitis, United States

<table>
<thead>
<tr>
<th></th>
<th>HAV</th>
<th>HBV</th>
<th>HCV</th>
<th>HDV</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acute infections</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(x 1000)/year*</td>
<td>125-200</td>
<td>140-320</td>
<td>35-180</td>
<td>6-13</td>
</tr>
<tr>
<td><strong>Fulminant deaths/year</strong></td>
<td>100</td>
<td>150</td>
<td>?</td>
<td>35</td>
</tr>
<tr>
<td><strong>Chronic infections</strong></td>
<td>0</td>
<td>1-1.25</td>
<td>3.5</td>
<td>70,000</td>
</tr>
<tr>
<td></td>
<td></td>
<td>million</td>
<td>million</td>
<td></td>
</tr>
<tr>
<td><strong>Chronic liver disease</strong></td>
<td>0</td>
<td>5,000</td>
<td>8-10,000</td>
<td>1,000</td>
</tr>
<tr>
<td>deaths/year</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Hepatitis C and B Virus

- **HCV** is a positive strand RNA virus
  - Genome is about 9.3kb, approximately the same size as HIV
  - No vaccine; therapy successful in 50% of people treated

- **HBV** is a DNA virus
  - Genome is very small, ~ 3.2kb,
  - Takes the form of a partially closed circle
  - Vaccine; therapy to control not cure
Treatment of HCV

- Two drugs are currently used to treat HCV infection
  - Interferon – \( \alpha \) (IFN), which is naturally made cytokine involved in protection against viral infections
  - Ribavirin (RBV), which is a nucleoside analog of guanosine. Its mechanism of action is controversial but it may act as a mutagen
Effects of Treatment

- Virus particles (called virions) are made in the liver but are transported throughout the body via the blood.
- Each virion contains one HCV RNA molecule that encodes the genome for the virus.
- Experimentalists can accurately measure the amount of HCV RNA per ml of blood (plasma or serum).
- Treatment should lower the amount of HCV RNA.
Acute Changes in HCV RNA Level Following First Dose of IFN-α

Mean Change in HCV RNA Level (Log<sub>10</sub>, eq/ml)

* significantly different compared to 5 mIU

Time after 1st dose of IFN

5 mIU
10 mIU
15 mIU
Mean Decrease in HCV RNA Levels Over First 14 Days of QD IFN-α Treatment

Lam N. DDW. 1998 (abstract L0346).
Model of HCV Infection

- **Infected Cell** (I) to **Target Cell** (T) via **Infection Rate** ($\beta$)
- **Virions/d** ($\rho$)
- **Loss** ($\delta$)
- **Clearance** ($c$)
What if IFN blocks infection?

I

\[ \text{clearance} \]

\[ \text{pvirions/d} \]

\[ \beta \]

\[ \rho \]

\[ \delta \]

\[ \text{death} \]

\[ \text{clearance} \]

Target cell

Infected Cell

IFN
What if IFN Blocks Production?

Infected Cell \( \xrightarrow{\delta} \) Death/Loss

\( \xrightarrow{\epsilon} \) Effectiveness

Clearance \( \xrightarrow{\gamma} \) Target Cell

\( \xrightarrow{IFN} \) Virions/d

\( \xrightarrow{\beta} \)
What if IFN blocks production?

- If IFN treatment **totally** blocks virus production, then
- \( \frac{dV}{dt} = -cV \implies V(t) = V_0 e^{-ct} \)
- Viral load should fall exponentially with slope \( c \). However, data shows an acute exponential fall followed by slower fall.
IFN Effectiveness in Blocking Production

- Let $\varepsilon = \text{effectiveness of IFN in blocking production of virus}$
  - $\varepsilon = 1$ is 100% effectiveness
  - $\varepsilon = 0$ is 0% effectiveness
- $\frac{dV}{dt} = (1 - \varepsilon)pI - cV$
Early Kinetic Analysis

- Before therapy, assume steady state so that \( pI_0 = cV_0 \). Also, assume at short times, \( I = \text{constant} = I_0 \), so that
  \[
  \frac{dV}{dt} = (1-\varepsilon)pI - cV = (1-\varepsilon)cV_0 - cV, \quad V(0)=V_0
  \]

- Model predicts that after therapy is initiated, the viral load will initially change according to:
  \[
  V(t) = V_0[1 - \varepsilon + \varepsilon \exp(-ct)]
  \]

- This equation can be fit to data and \( c \) and \( \varepsilon \) estimated.

- Thus drug effectiveness can be determined within the first few days!
## Viral Kinetics of HCV Genotype 1

<table>
<thead>
<tr>
<th>Drug Efficacy</th>
<th>Viral Clearance Constant (1/d)</th>
<th>Half-life of Virions (Hours)</th>
<th>Production &amp; Clearance Rates ($10^{12}$ Virions/d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5MU</td>
<td>81 ± 4%</td>
<td>6.2 ± 0.8</td>
<td>0.4 ± 0.2</td>
</tr>
<tr>
<td>10MU</td>
<td>95 ± 4%</td>
<td>6.3 ± 2.4</td>
<td>2.3 ± 4</td>
</tr>
<tr>
<td>15MU</td>
<td>96 ± 4%</td>
<td>6.1 ± 1.9</td>
<td>0.6 ± 0.8</td>
</tr>
</tbody>
</table>
Standard Model of HCV Dynamics

**Equations**

\[
\frac{dT}{dt} = \lambda - dT - \beta VT \\
\frac{dI}{dt} = \beta VT - \delta I \\
\frac{dV}{dt} = (1 - \varepsilon)pI - cV
\]

**Parameters**

- \( \lambda \) Supply of target cells
- \( \delta \) Net loss rate of target cells
- \( \beta \) Infectivity rate constant
- \( \delta \) Infected cell death rate
- \( \varepsilon \) Drug efficacy
- \( p \) Virion production rate
- \( c \) Virion clearance rate constant

**Variables**

- \( T \) Target Cell Density
- \( I \) Infected Cell Density
- \( V \) Virus Concentration

**Initial Conditions**

\( T(0) = T_0 \quad V(0) = V_0 \quad I(0) = I_0 \)
Assume Steady State

- Before treatment patient is generally in a steady state.

\[
\frac{dI}{dt} = \beta V_0 T_0 - \delta I_0 = 0
\]

\[
\frac{dV}{dt} = pI_0 - cV_0 = 0
\]

Hence

\[
\beta V_0 T_0 = \delta c V_0 / p \quad \text{or} \quad \beta T_0 = \delta c / p
\]

and

\[
\frac{dI}{dt} = \beta V T_0 - \delta I = \delta (c / p) V - \delta I
\]

\[
\frac{dV}{dt} = pI - cV
\]
Solution: Change in Viral Load

- Assuming $T = T_0 = \text{constant}$,

\[
V(t) = \frac{1}{2} V_0 \left[ (1 - \frac{c + \delta - 2\varepsilon c}{\theta}) e^{-\lambda_1(t-t_0)} + (1 + \frac{c + \delta - 2\varepsilon c}{\theta}) e^{-\lambda_2(t-t_0)} \right]
\]

where

\[
\lambda_1 = \frac{1}{2} (c + \delta + \theta) \quad \lambda_2 = \frac{1}{2} (c + \delta - \theta) \quad \theta = \sqrt{(c - \delta)^2 + 4(1 - \varepsilon)c\delta}
\]

- When $c \gg \delta$, $\lambda_1 \approx c$ and $\lambda_2 \approx \varepsilon\delta$
Days

Log$_{10}$ HCV RNA/mL

Days

Log$_{10}$ HCV RNA/mL
## Viral Kinetics of HCV Genotype 1

<table>
<thead>
<tr>
<th>Drug Efficacy</th>
<th>Second Phase Decay Constant, $\delta$ (1/d)</th>
<th>Half-life of Infected Cells (Days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5MU 81 ± 4%</td>
<td>0.09 ± 0.14</td>
<td>2.2–69.3</td>
</tr>
<tr>
<td>10MU 95 ± 4%</td>
<td>0.10 ± 0.05</td>
<td>4.3–17.3</td>
</tr>
<tr>
<td>15MU 96 ± 4%</td>
<td>0.24 ± 0.15</td>
<td>1.7–6.3</td>
</tr>
</tbody>
</table>
High Second-Phase Slope Is Predictive of HCV Being Undetectable at 12 Weeks
HCV Viral Kinetics: Summary

- Biphasic clearance of serum HCV RNA
- 1st phase rapid; depends on IFN-α dose
  - This appears to be due to dose-dependent efficacy in blocking HCV production
- 2nd phase slower. Slope appears to be a measure of rate of infected cell loss