Immunologic Benefits of Enfuvirtide despite Virologic Failure due to the Emergence of Resistance

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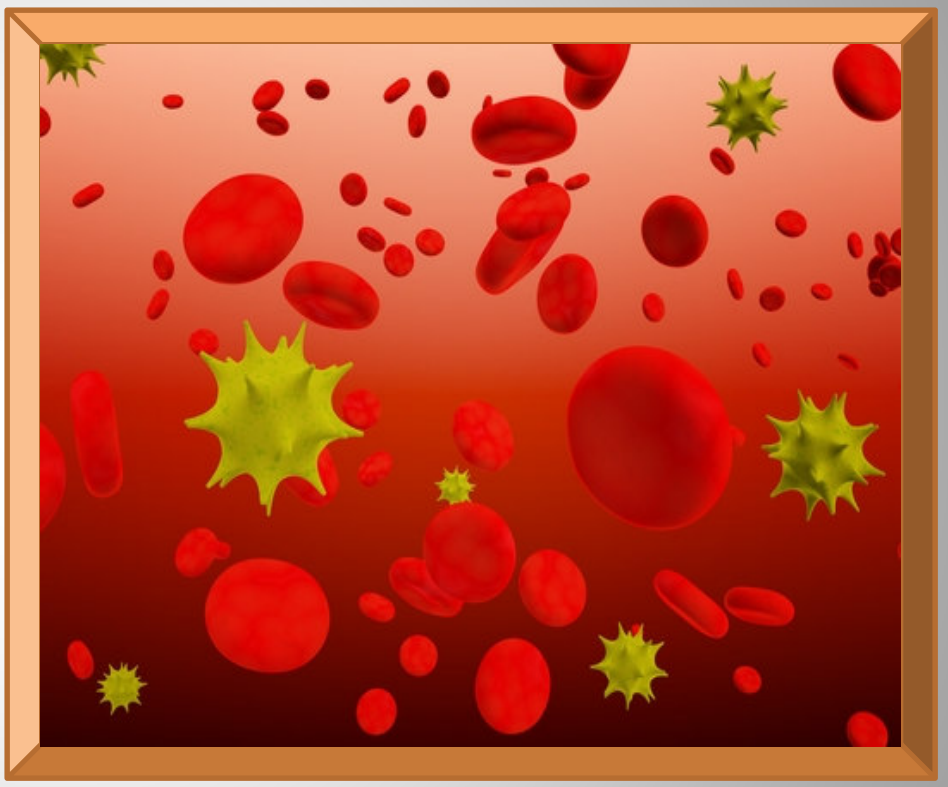


Outline

- Introduction: HIV Infection
- Data and Research Questions
- Enfuvirtide
- Model and data fitting
- Results and Discussion
- Conclusion

Introduction: HIV Infection

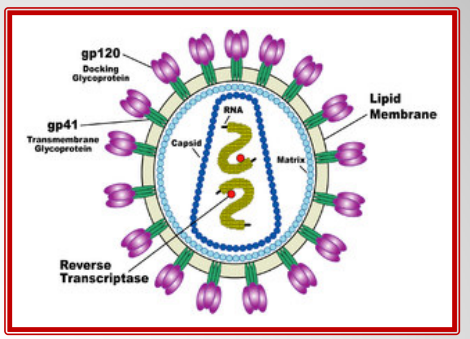
- **HIV: Human Immunodeficiency Virus that can lead to AIDS**

- **HIV Epidemiology:**
  - WHO and UNAIDS Estimates:
    - 33.4 millions people living with HIV at the end of 2008
    - 2.7 millions newly infected (2008)
    - 2.0 millions AIDS death including 280,000 children (2008)
  - Means of Transmission:
    - Sexual contact
    - Blood or blood products
    - Mother to child
  - Transmission probability
    - Depends on route

Introduction: HIV Infection

❖ **HIV Immunology:**

- Structure:

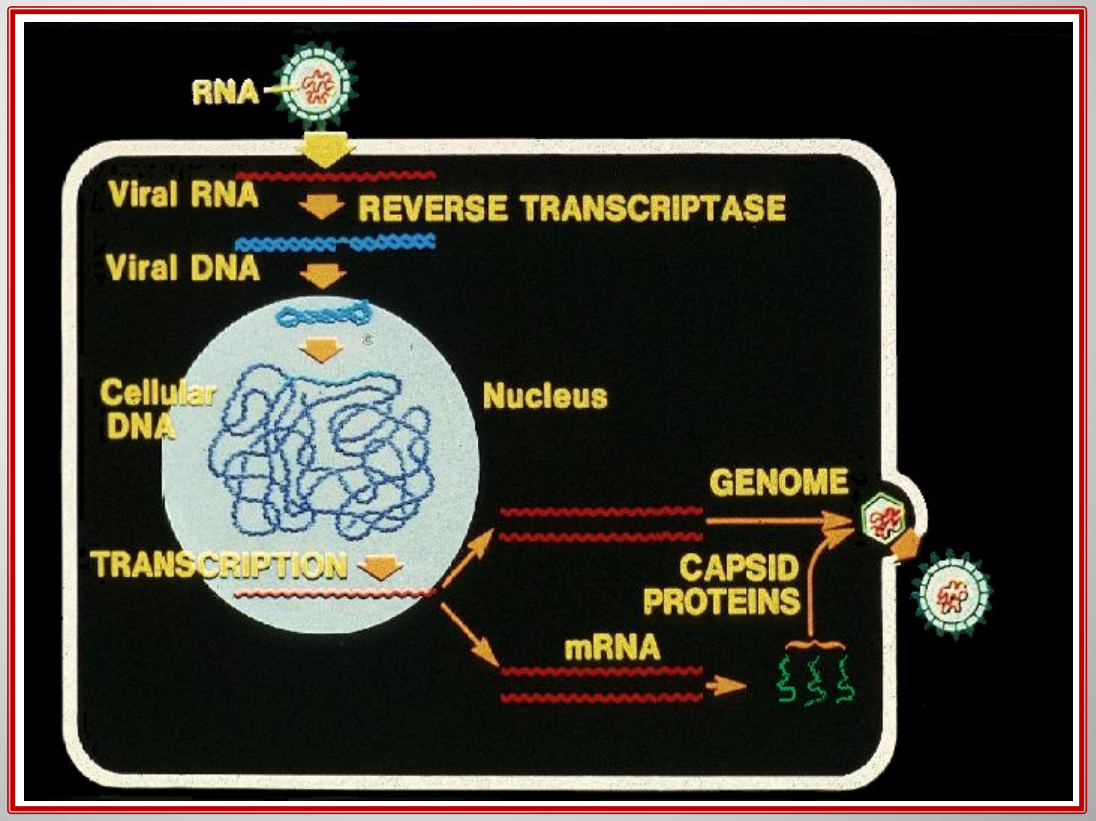


- Tropism:
  - Variety of immune cells (mainly CD4$^+$ T cells PLUS macrophages and dendritic cells)
- Loss of CD4$^+$ T cells:
  - Killing by virus
  - Apoptosis
  - Killing by Cytotoxic Lymphocytes (CTL)
- CD4$^+$ T cell count:
  - Disease stage (> 500, 200 – 500, <200 cells/mm^3)
  - Treatment decision (> 350; 200-350, < 200 cells/mm^3)

Introduction: HIV Infection

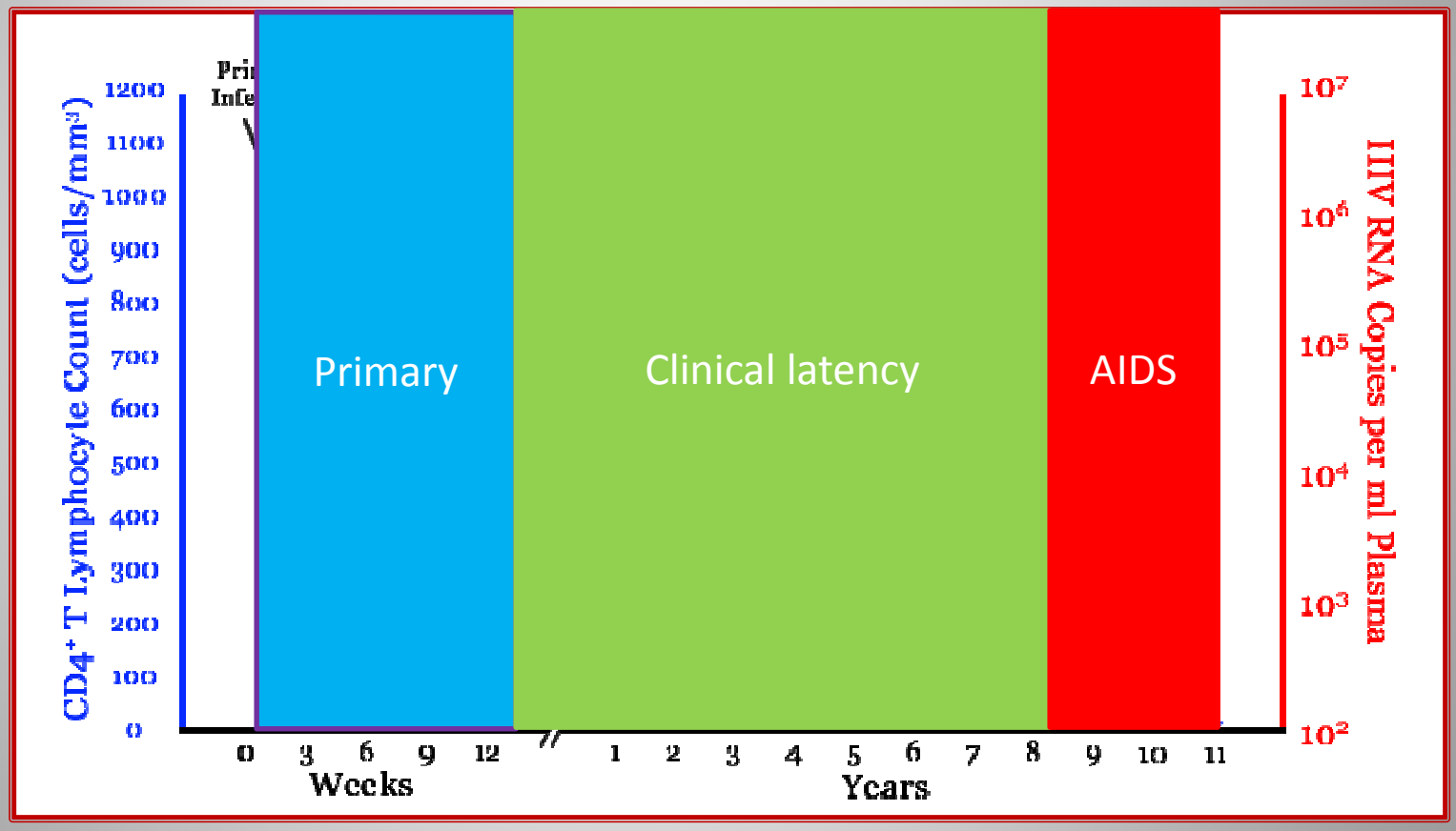
❖ **HIV Immunology (contd …):**

- Viral replication cycle:

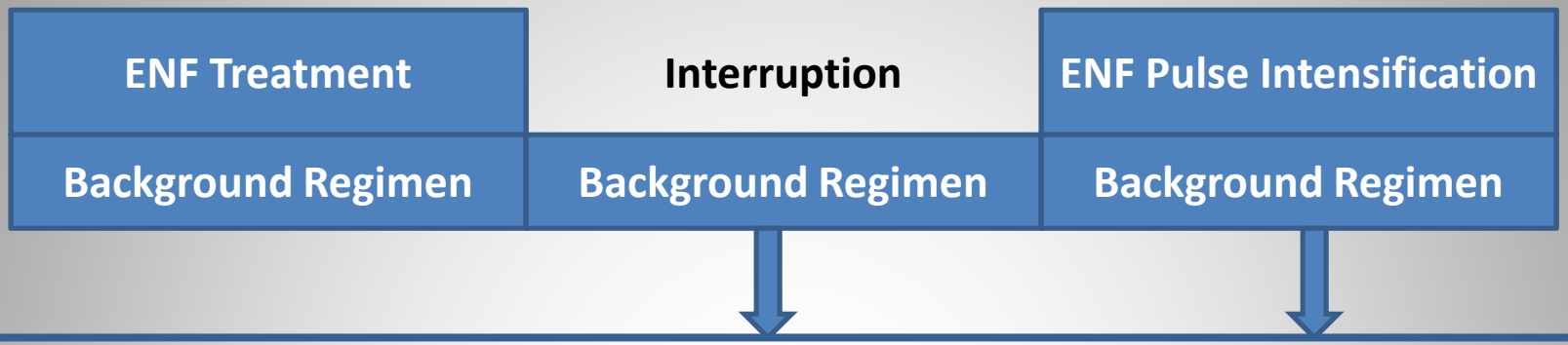


Introduction: HIV Infection

❖ **HIV Immunology (contd …):**

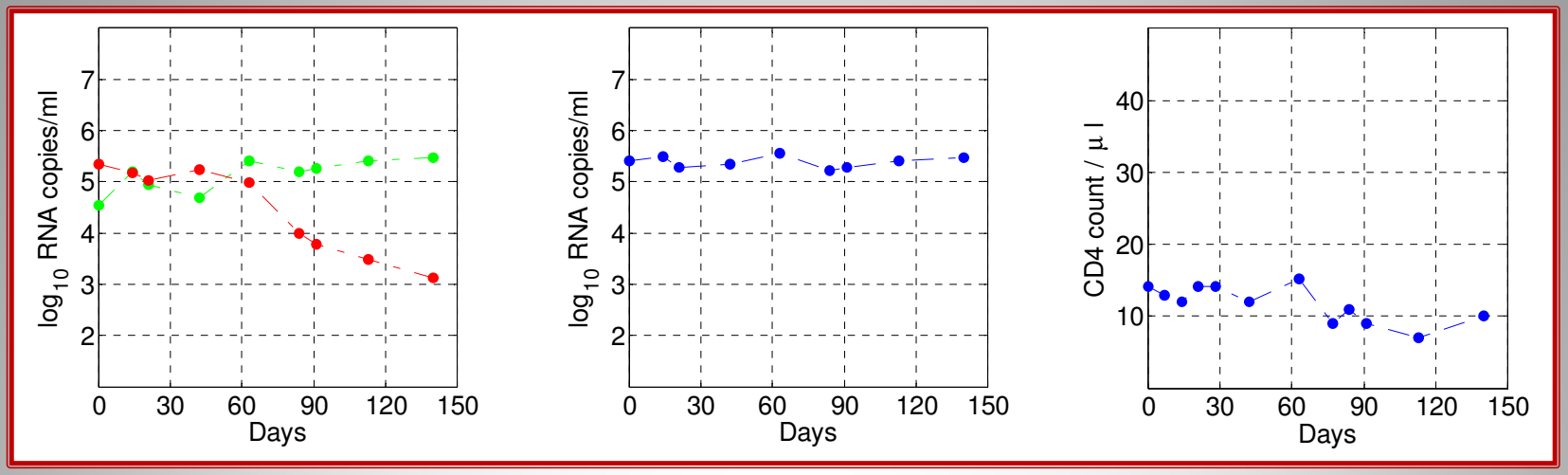


Data & Research Questions



- ❑ Viral load (University of California, San Francisco)
- ❑ $CD4^+$ T cell count (University of California, San Francisco)
- ❑ Proportion of ENF resistant (V38A mutant) virus (Harvard Medical School)

Data & Research Questions



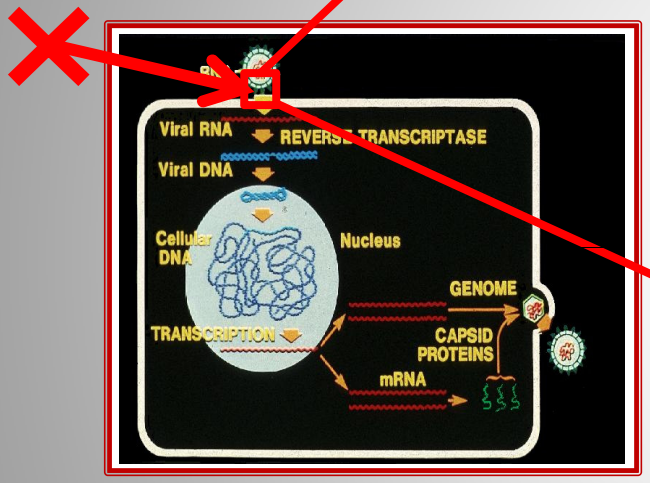
❖ **Questions:**

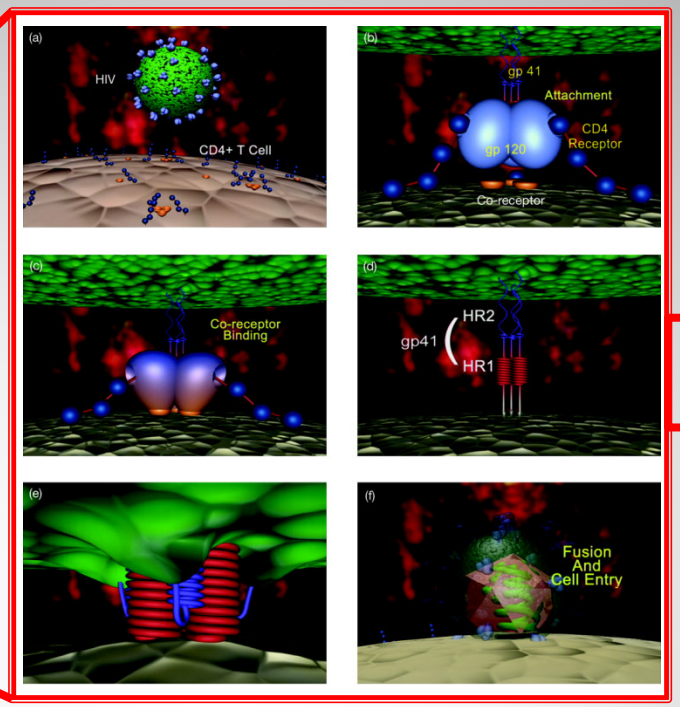
1. Resistant virus wanes rapidly with a rapid growth of wild-type virus. What factors play roles in virus population turnover?
2. Total viral remains almost constant. Effect of fitness? What factors play a role in determining plasma viral load?
3. Benefits of Re-administering or continuing drugs in the presence of resistance?

Enfuvirtide

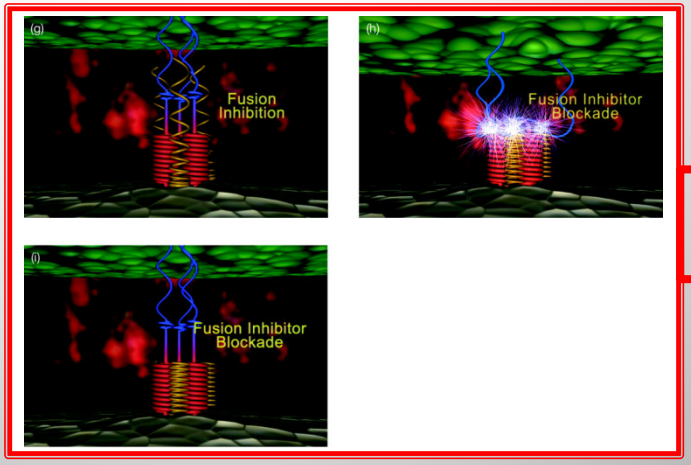
- The only FDA approved fusion inhibitor
- Expensive and must administered parentally
- It is often reserved for heavily pretreated patients with limited therapeutic options
- Highly effective if given in combination with 2 or more ART
- Emergence of resistance resulting in substantial decrease in antiviral activities
- Virologic failures often have a consequence of ENF interruption

Enfuvirtide



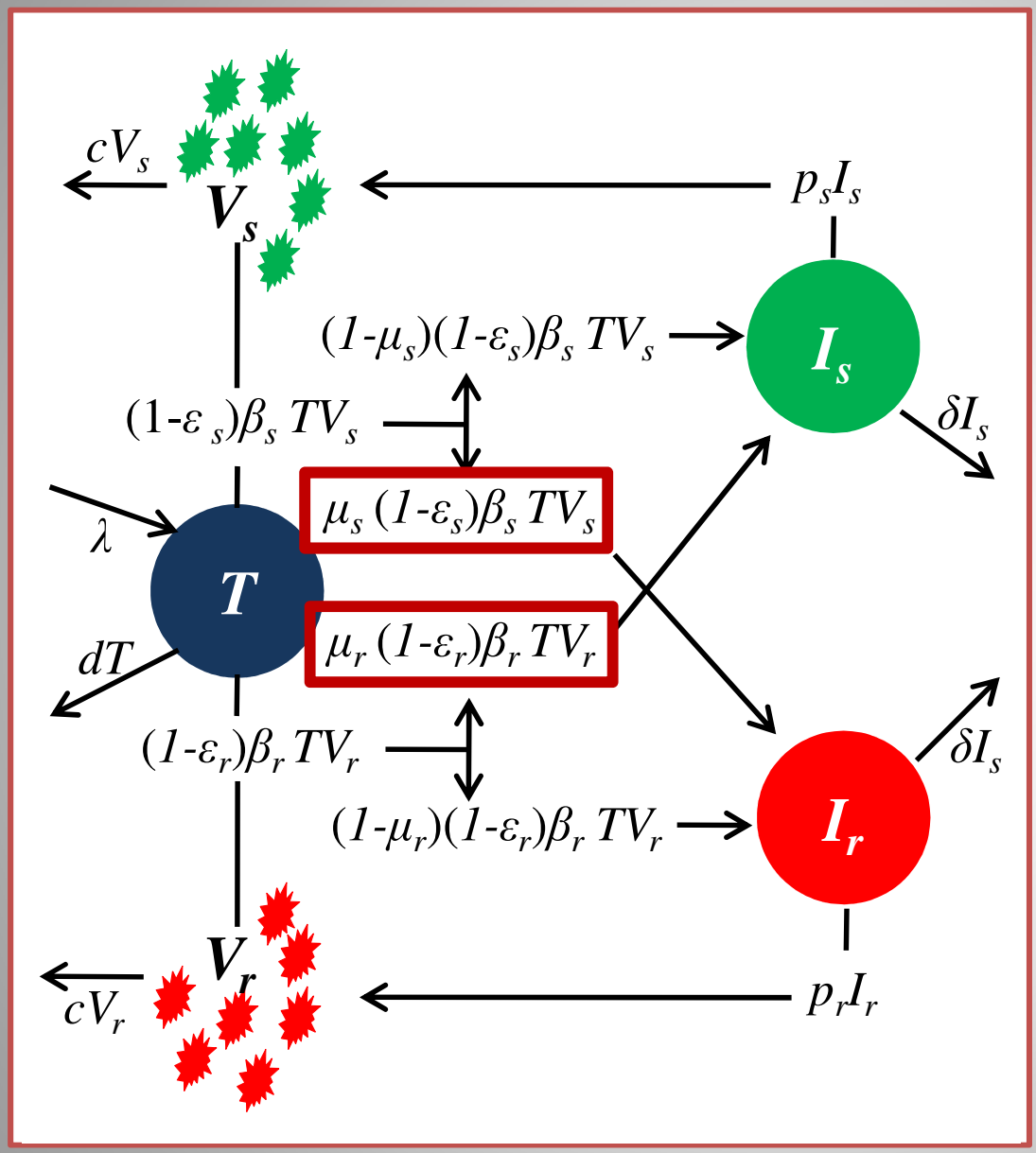


Without ENF



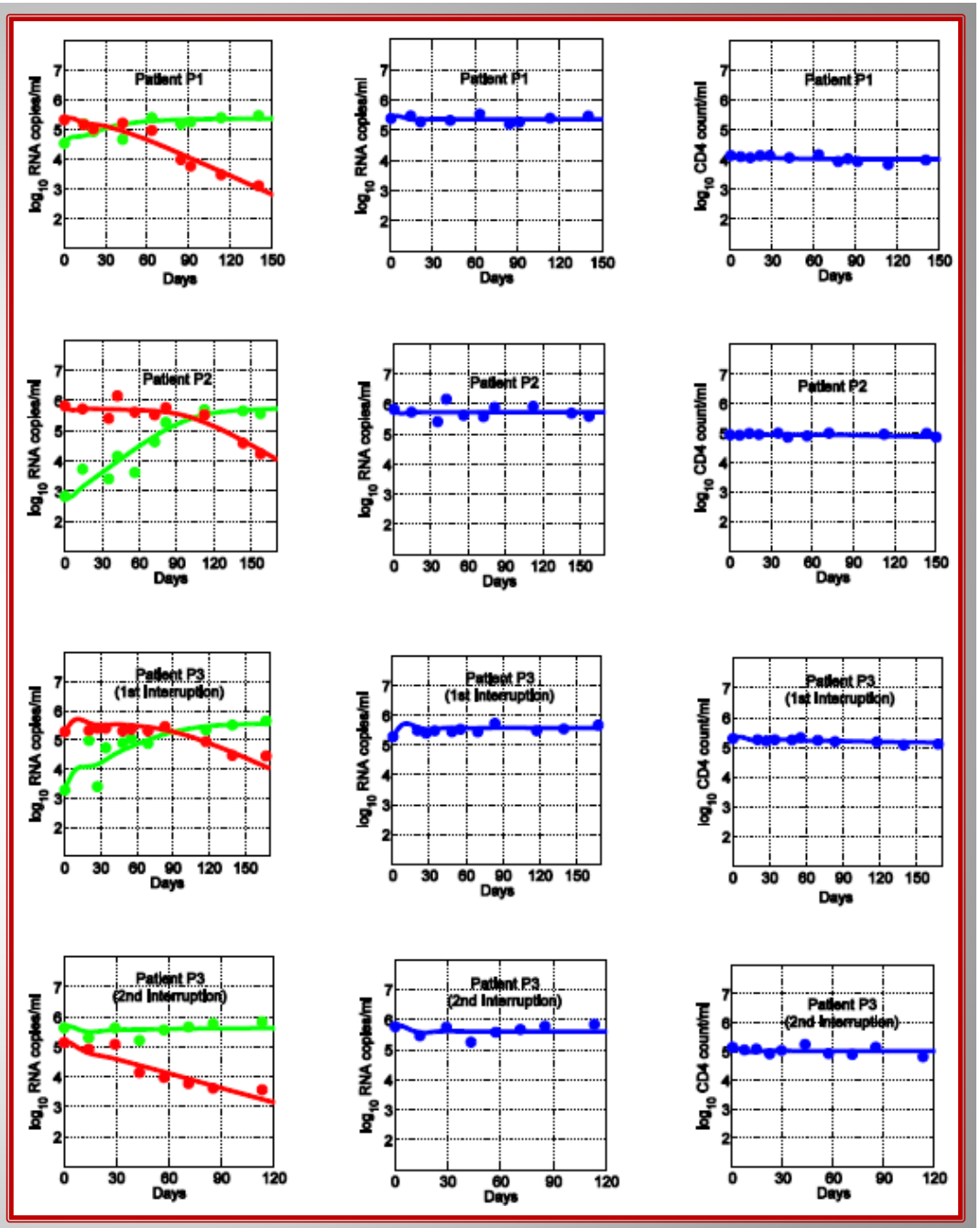
With ENF

Model & Data Fitting

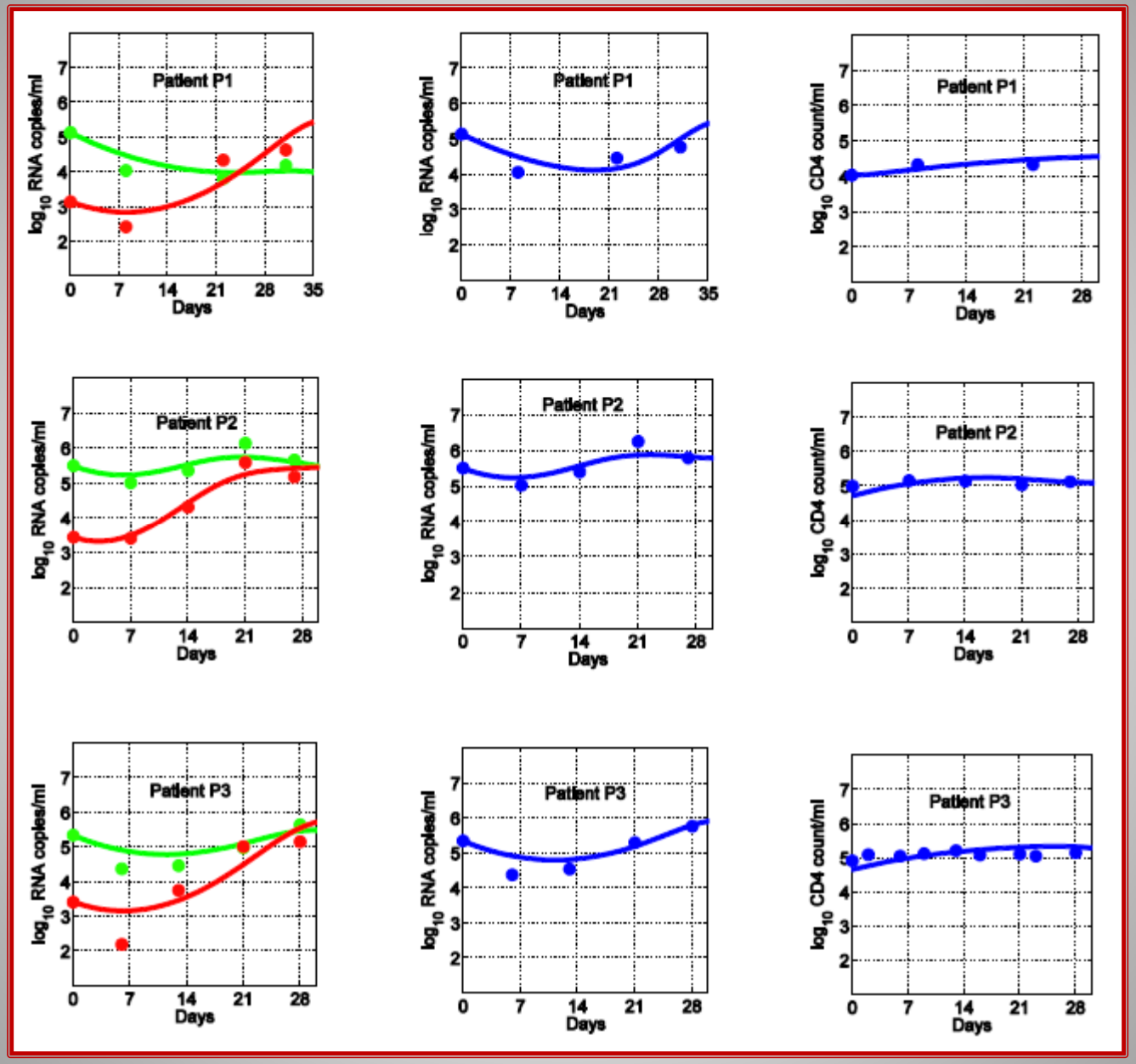


$$\beta_r = (1-\alpha)\beta_s$$

❖ Data Fitting - Interruption:



❖ Data Fitting - Readministration:



Result & Discussion

❖ **Resistance Virus waning during Enterruption:**

- Backward and forward mutation rates are comparable:

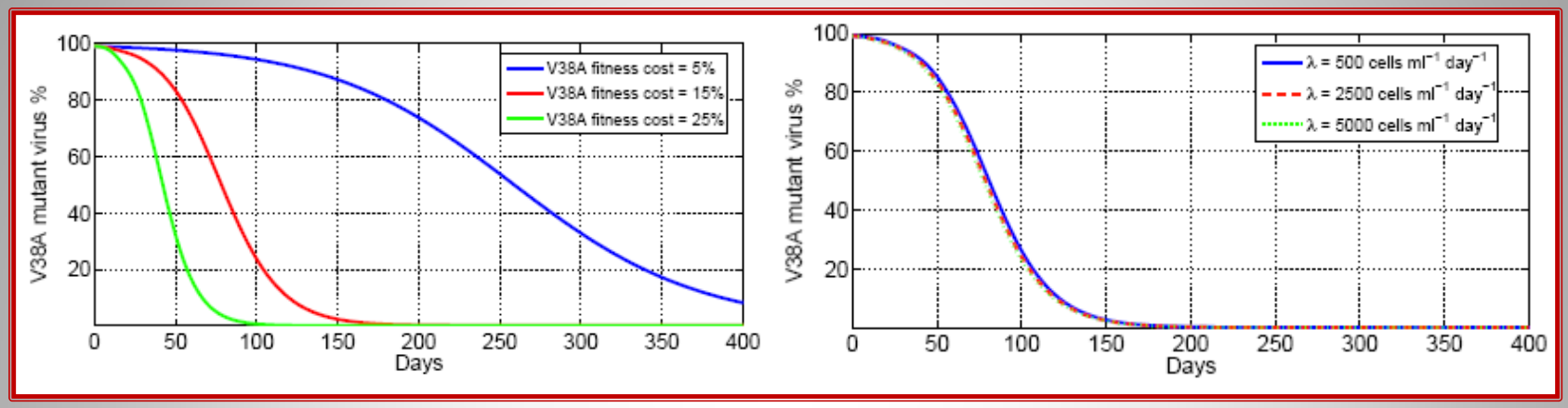
  $\mu_s = 2.24 \text{ X } 10^{-5}$ & $\mu_r = 1.73 \text{ X } 10^{-5}$

  Loss of resistance virus due to backward mutation = 26 virions per ml per week or 70 virions per ml per month

- Fitness cost: $\alpha = 0.17$

Result & Discussion

- Fitness cost is a leading cause of the waning of resistance virus

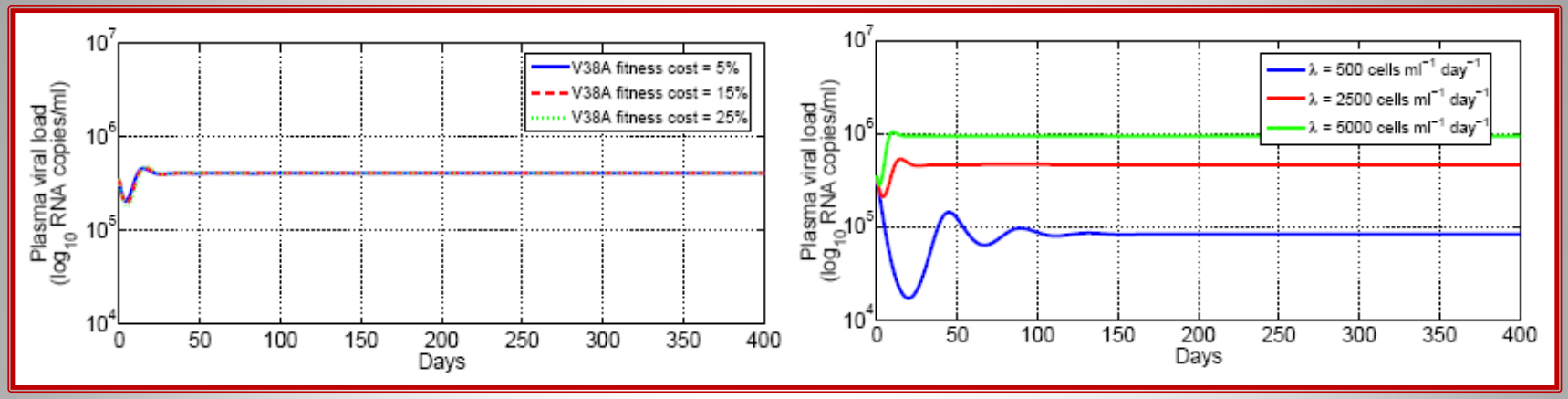


- Time to the viral turnover from the interruption:

$$t_\theta = \frac{(1-\alpha)(1-\mu_r)(1-\varepsilon_r)}{\alpha\delta} \ln \frac{r(0)}{r(t_\theta)}$$

Result & Discussion

❖The total plasma viral load:



➢Steady state:

$$\bar{V} = \frac{p\lambda}{c\delta} - \frac{d}{(1-\mu_s)\beta_s}$$

Result & Discussion

❖ **Benefits of ENF:**

➢ ENF efficacy to sensitive virus:

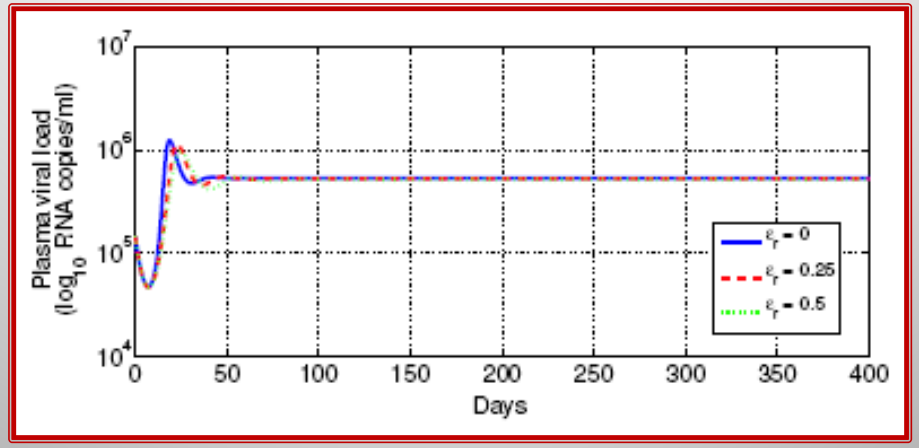
$\varepsilon_s = 0.66$

➢ ENF efficacy to resistant virus:

$\varepsilon_r = 0.29$

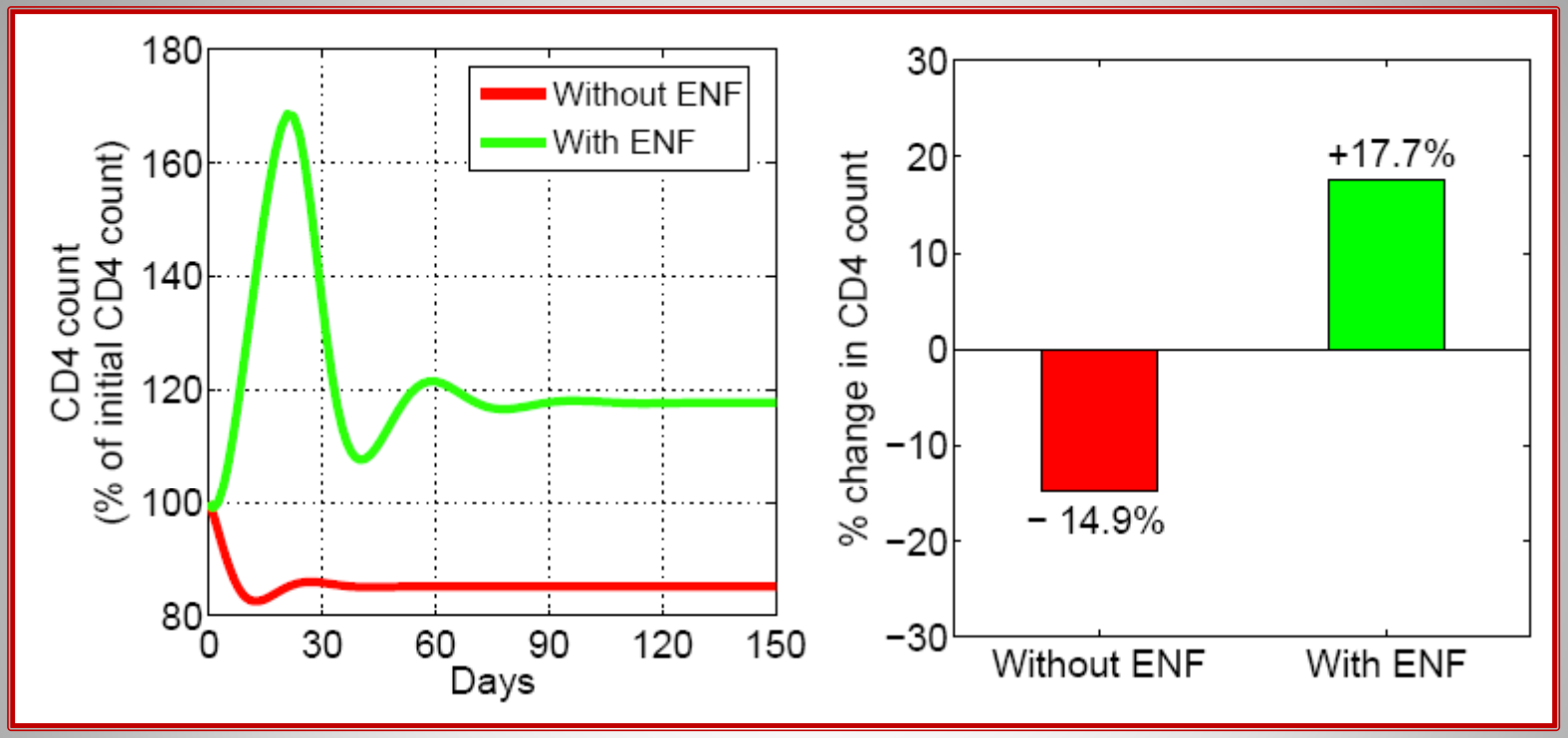
➢ The Viral load:

$$\bar{V}_E = \frac{p\lambda}{c\delta} - \frac{d}{(1-\mu_r)(1-\varepsilon_r)(1-\alpha)\beta_s}$$



Result & Discussion

➢Immunologic benefit:



➢Uninfected T-cell:

$$\bar{T}_E = \frac{\delta c}{(1-\mu_r)(1-\varepsilon_r)(1-\alpha)\beta_s p_s}$$

Conclusion

- There is negligible contribution of continued evolution (and mutation) on virus population turnover.
- Fitness cost is the most important factor for the waning of resistant virus during drug-interruption. Drug-efficacy to resistant virus is also important for virus population turnover during drug Re-administration.
- Fitness cost does not affect the plasma viral load level. The plasma viral load is primarily determined by the combined term ($p\lambda/c\delta$) of few viral dynamic parameters.
- Despite virologic failures, there may be immunologic benefits on re-administering or/and continuing the drug.

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Data

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