A Mathematical Model that Predicts Virological Failure and Elucidates the Impact of Lymph Node Drug Penetration

June 16, 2017

Steven Sanche\textsuperscript{1}, Nancy Sheehan\textsuperscript{1,2}, Thibault Mesplède\textsuperscript{1,3}, Mark Wainberg\textsuperscript{1,3}, Jun Li\textsuperscript{1}, Fahima Nekka\textsuperscript{1}

\textsuperscript{1}: Faculty of Pharmacy, Université de Montréal
\textsuperscript{2}: Chronic Viral Illness Service, McGill University Health Centre
\textsuperscript{3}: McGill University AIDS Centre, Jewish General Hospital
BACKGROUND

Predicting the outcome of an HIV treatment

• Clinical trial results: gold standard

• **Hard to predict** patients’ outcome when **specific context** hasn’t been studied in a clinical trial (e.g. patient specific mutation, adherence level)

```
• Pharmacokinetics
• Pharmacodynamics
• Immune response
```
To develop a model to help understand and predict treatment failure and resistance
OBJECTIVE

More precisely

Not model everything, model the most important processes linking drug use to viral loads

The model

Time sequence of drug intake

Viral Loads
A physiological compartment

Modeled processes

Rx action

Productive cell death

Immunity CD8+ FDC

Infection After de novo mutation

Infection

Natural CD4+ death

Fitness cost

New CD4+

Equations can describe how this system will evolve over time.
METHODS

A model for viral kinetics — No Rx

\[
\frac{dx}{dt} = \lambda - \sum_{i=1}^{n} \beta_i x y_i - d_x x
\]

\[
\frac{dy_i}{dt} = \beta_i x (t - \tau) y_i (t - \tau) e^{-d_x \tau} + A_i - d_y y_i
\]

\[
\frac{dv_i}{dt} = k_i y_i - d_v v_i
\]

\[x: \text{number of CD4+ susceptible to be infected}\]

\[y: \text{number of CD4+ producing virions}\]

\[v: \text{number of virions}\]

\[\text{Index } i: \text{identifies the strain}\]

Rosenbloom et al. (2014) Nature Medicine
Sanche et al. (2017) CPT: pharmacometrics and Quantitative Systems
METHODS

What about Rx action?

• Modulates the rate of infection
• Based on *in vitro* data

\[ f_a = 1 - \frac{1}{1 + \left( \frac{C_p}{IC_{50}} \right)^m} \]

But how do we use to extrapolate this *in vitro* data to the *in vivo* context?
METHODS

HYPOTHESES

To fill in the knowledge gaps and complete the model...

- **H_p**: most cells within the host that are susceptible to infection are as exposed to drugs as *peripheral blood* mononuclear cells.

- **H_i**: there is at least one physiological compartment harboring a significant number of infection events that is much less exposed to the drug, and this is the *lymph node*.
METHODS

Parameter values

• All parameter values obtained *a priori*

• Plasma protein binding
  Acosta et al. (2012) *Antimicrobial agents and chemotherapy*

• Lymph node drug penetration
  Fletcher et al. (2014) *PNAS*
METHODS

Changes to Rosenbloom et al. model

• Plasma protein binding
• Lymph node drug penetration
• Eclipse phase
• Distribution for parameter values
  Rate of viral replication \textit{in vivo}
  Quasispecies variation in IC50
  Adherence model

\[ f_a = 1 - \frac{1}{1 + \left( \frac{C_p}{kl \, kp \, IC_{50}} \right)^m} \]
<table>
<thead>
<tr>
<th>Treatment</th>
<th>Clinical observations</th>
<th>Prediction (H0)</th>
<th>Prediction (H1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efavirenz Monotherapy</td>
<td>Resistance</td>
<td>Little to no resistance</td>
<td>90% Resistance</td>
</tr>
<tr>
<td></td>
<td>Mostly virological</td>
<td>Virological success for most individuals</td>
<td>Mostly virological failures</td>
</tr>
<tr>
<td></td>
<td>failures</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atripla</td>
<td>Virological failure 14%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Darunavir/ Ritonavir</td>
<td>Virological failure 0%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Virological failure ~15%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
LIMITATIONS

- Availability of Lymph Node drug penetration data...
- Other sanctuary (Rx) sites?
- So far, only virological success/failure, not viral loads
- Immune system action (bundled up parameter)
CONCLUSION

So …

**Lymph node**: can potentially account for most cases of virological failure with resistance

A model for *extrapolation*!

Can be used for individualized predictions:

- Adherence patterns
- Individual PK parameter
- Quasi-species susceptibility to drugs
- Diverse mutations
- Viral growth rate during rebounds
THANK YOU! QUESTIONS?

Supervisors
Fahima Nekka
Jun Li

Other collaborators
Nancy Sheehan
Thibault Mesplède
Mark Wainberg

Fellow students
Guillaume Bonnefois
Sara Soufsaf
Abdullah Aljutayli
Morgan Craig

Correspondance: steven.sanche@gmail.com

Industrial Chair in Pharmacometrics
In honor of Dr. Mark Wainberg