HIV-1 dynamics under integrase inhibitor therapy suggests a subset of cells with slow integration

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Modeling viral load decay under ART
Decay under integrase inhibitor (InSTI)
Models to try to understand this pattern

• Murray et al. AIDS 2007
• Sedaghat et al. PNAS 2008
• Sedaghat et al. Antiviral Therapy 2009
• Spivak et al. AIDS Res Hum Ret 2011
• Gilmore et al. PLoS Comp Biol 2013

All based on original data from Murray et al. 2007
Data sets

• Combination boosted PI LPV/r, and RTIs EFV, 3TC and TDF (600/300/300 mg QD)
  • Eight participants
  • VLs at 6h intervals for 72 h, daily until day 10, and then weekly until day 28

• Original RAL monotherapy dose ranging study (100-600mg BID)
  • Twenty eight HIV-1-infected, ARV-drug naïve participants
  • VLs at 0, 6, 12, 24, 48h and then on days 3, 4, 7, 9

• Combination RAL (400mg BID) + FTC/TDF (200/300mg  QD)
  • Eleven participants of the viral dynamics substudy of ACTG A5248
  • VLs at 0, 2, 4, 6, 12, 18, 24, 30, 36, 42, 48h and then on days 3, 4, 7, 10, 14, 21 & 28

Data from Markowitz et al. JV 2003; Markowitz et al. JAIDS 2006; Andrade et al. JID 2013
Data sets

• Combination boosted PI lopinavir-ritonavir and RTIs efavirenz, LAM and TDF (600/300 QD)
  • Eight participants
  • VLs at 6h intervals for 72 h, daily until day 10, and then weekly until day 28

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Data from Markowitz et al. JV 2003; Markowitz et al. JAIDS 2006; Andrade et al. JID 2013

47 HIV-1 infected patients
613 viral load data points
Early phase of decay under RAL

Andrade et al. AIDS 2015
Model to analyze the early decay
Parameters from data fits (early decay)

<table>
<thead>
<tr>
<th>$k$</th>
<th>Mono</th>
<th>Comb</th>
<th>$\delta_1$</th>
<th>$\delta_2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.8</td>
<td>0.995 (0.001)</td>
<td>0.910 (0.034)</td>
<td>0.19 (0.04)</td>
<td>0.91 (0.05)</td>
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<tr>
<td>2.6</td>
<td>0.997 (0.001)</td>
<td>0.940 (0.027)</td>
<td>0.15 (0.04)</td>
<td>0.89 (0.04)</td>
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<tr>
<td>3.3</td>
<td>0.997 (0.001)</td>
<td>0.939 (0.025)</td>
<td>0.12 (0.04)</td>
<td>0.89 (0.04)</td>
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</table>
Model for the decay of viral load under RAL
Model for the decay of viral load under RAL
Fits of the model

Quad Tx (No RAL)
RAL combination
Model results

The graph illustrates the dynamics of HIV RNA copies/mL over time (days). The x-axis represents time in days, ranging from 0 to 30, and the y-axis represents HIV RNA copies/mL, ranging from $10^1$ to $10^5$. The graph shows three phases:

- **Phase 1a**: The initial rapid decline in HIV RNA copies/mL.
- **Phase 1b**: A slower, more gradual decline.
- **Phase 2**: A further, significant drop in HIV RNA copies/mL, expressed by the equation $\sim 1 - (1 - \omega)e^{\omega \beta t}$.

Different lines represent various treatment regimens:

- **Quad treatment**: Represented by a blue line.
- **RAL combination therapy**: Represented by a red line.
- **RAL monotherapy**: Represented by a green line.

The graph highlights the impact of different treatments on reducing HIV RNA levels over time.
Model for the decay of viral load under RAL
Final model
Conclusions

• HIV-1 infection is sustained by short-lived infected cells (fast integration and a short viral production period,) and by long-lived infected cells (slow integration but an equally short production period).

• Infection of long-lived cells represent ~4% of productive infection events.

• In short-lived cells the pre-integration has t½ ~7 hours, long-lived cells t½ ~6 wks.

• Efficacy of RAL is estimated by the difference in viral load at the start of the second phase in protocols with and without RAL.

• We provide a mechanistic model of viral infection that parsimoniously explains the kinetics of viral load under multiple classes of antiretrovirals.
Acknowledgments

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• John Mellors

Brigham and Women’s Hospital
• Daniel R. Kuritzkes

M. Markowitz / D. Ho

Merck Sharp & Dohme
Parameter estimates

<table>
<thead>
<tr>
<th></th>
<th>Exponential models</th>
<th>Viral kinetics model*</th>
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<tbody>
<tr>
<td>Phase 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1a</td>
<td></td>
<td>( \delta_2 = 0.85 )</td>
</tr>
<tr>
<td>1b</td>
<td></td>
<td>( \delta_1 + (1-\omega)k_1 = 0.39 )</td>
</tr>
<tr>
<td>Phase 2</td>
<td></td>
<td>( \delta_{M1} + (1-\omega)k_1 = 0.02 )</td>
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</table>
(Constrain the parameters to facilitate fits)
Heuristic mixed-effects model fitting

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<thead>
<tr>
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<tbody>
<tr>
<td></td>
<td>RAL</td>
<td>No-RAL</td>
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<tr>
<td>Phase 1</td>
<td>1a</td>
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<tr>
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<tr>
<td>Phase 2</td>
<td></td>
<td>0.045</td>
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Timing the Lifecycle (in vitro)

Estimated time between different phases of HIV-1 lifecycle. The time from reverse transcription to integration is ~9 h (comparing the peak of activity, “+”), but there is a large uncertainty (shaded area corresponds to 98% quantile for each phase).

Data and figure from Mohammadi et al., PLoS Path. (2013)
Timing the Lifecycle (in vivo)

Estimated time between different phases of HIV-1 lifecycle, from mathematical analyses of viral load dynamics under treatment.

Data and figure from Murray et al., J. Virol. (2011)