MATHEMATICAL MODELING OF PREDICTORS OF POSTTREATMENT CONTROL IN HIV CURE TRIALS

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Introduction

- Analytical treatment interruptions (ATI) are used to understand the potential of curative interventions in clinical trials.
- To protect the study participant and his or her partners, ATIs should be designed to minimize the time off of ART, with therapy resumed as soon as it becomes likely that post-treatment control will likely not be achieved.
- We used an ensemble of modeling approaches and data from ACTG and Gilead ATI studies to identify early predictors for participants who will control their virus off ART.

Methods: Overview

Data
- NHP rebound
  - TLR7/vaccine studies
  - N=70
- Clinical rebound
  - ACTG cohorts
  - TLR7 trial
  - N=134

Predictive Modeling
- Data split into training and validation data sets
- Mathematical modeling & machine learning

Derivation and Testing
- Predictors of control
  - Learn and characterize predictors with train set
  - Evaluate sensitivities of predictors
- Validation
  - Validate predictors with validation data set

Clinical Utility
- Real-time calculator
- ART re-start criteria guidance for protocols

ACTG, AIDS Clinical Trial Group; ATI, analytical treatment interruption; NHP, nonhuman primate; TLR7, toll-like receptor 7.
Methods: Modeling and Machine Learning

[A] Study participant data

- Learn and characterize
- Predict events

[C] Ranking of Predictors

Approach:
1. Apply modeling and machine learning
2. Characterize predictors
3. Test sensitivities

[D] Machine Learning

[B] Modeling

- Peak
- Slope-1
- Slope-2
- Set point
- Time to Rebound

NC, noncontrollers; C, controllers.
Results: SIV and HIV Viral Dynamics of Control

Example ART Re-start Criteria (ACTG):
- VL ≥1000 c/mL for 4 weeks
- No drop of 0.5 log from previous week

Definitions: Controller
- HIV: Post ART VL ≤400 c/mL at 2/3 of time points for ≥24 weeks

SIV

Non-controllers

Controllers

N=70

HIV

N=134

SIV (1000 c/mL)

Sensitivity 0.15
Specificity 1.00
Accuracy 0.84
PPV 1.0
NPV 0.84

HIV (1000 c/mL)

Sensitivity 0.83
Specificity 0.54
Accuracy 0.68
PPV 0.18
NPV 0.97

NPV, negative predictive value; PPV, positive predictive value; SIV, simian immunodeficiency virus; VL, viral load.

Borducchi et al., 2016 Nature; Namazi et al., 2018 JID
## Results: Sensitivity Scores for Predictors of Control

<table>
<thead>
<tr>
<th></th>
<th>Early Best 3*</th>
<th>Peak</th>
<th>Slope 1</th>
<th>Time to Rebound</th>
<th>Peak + Slope 1</th>
<th>Peak + Time to Rebound</th>
<th>Slope 1 + Time to Rebound</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>0.94</td>
<td>0.78</td>
<td>0.39</td>
<td>0.22</td>
<td>0.83</td>
<td>0.89</td>
<td>0.61</td>
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<tr>
<td>Specificity</td>
<td>0.94</td>
<td>0.99</td>
<td>0.97</td>
<td>0.97</td>
<td>0.98</td>
<td>0.95</td>
<td>0.94</td>
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<tr>
<td>Accuracy</td>
<td>0.94</td>
<td>0.88</td>
<td>0.68</td>
<td>0.60</td>
<td>0.91</td>
<td>0.92</td>
<td>0.78</td>
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<tr>
<td>PPV</td>
<td>0.74</td>
<td>0.93</td>
<td>0.70</td>
<td>0.57</td>
<td>0.88</td>
<td>0.76</td>
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<tr>
<td>NPV</td>
<td>0.99</td>
<td>0.96</td>
<td>0.90</td>
<td>0.88</td>
<td>0.97</td>
<td>0.98</td>
<td>0.93</td>
</tr>
<tr>
<td>Prev</td>
<td>0.1513</td>
<td>0.1513</td>
<td>0.1513</td>
<td>0.1513</td>
<td>0.1513</td>
<td>0.1513</td>
<td>0.1513</td>
</tr>
</tbody>
</table>

*Early predictors = Time to Rebound + Slope 1 + Peak.
Prev, prevalence of controllers in dataset.
Conclusion

- This study identified predictors that can easily be derived using clinical data as it is being collected in real time; these parameters can predict HIV post-treatment control (and non-control)

- The key predictors are (i) Viral Peak, (ii) Time to Rebound, and (iii) Rate of Viral Rebound (Slope-1); when used in combination, these predictors have high accuracy, sensitivity, and specificity scores
  - (i) ≥94% (Peak + Slope-1 + Time to Rebound), (ii) ≥89% (Peak + Time to Rebound), and (iii) ≥78% (Peak only)

- Incorporating these predictors within ART restart criteria may allow participants who are not likely to become controllers to restart ART without delay

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