Predicting treatment outcomes using rich adherence data & antiretroviral pharmacometrics

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Regimen & Adherence

Pharmacokinetics, Pharmacodynamics,
Drug resistance, Replication capacity, Immune effects,
Other host factors, Other viral factors...

Virologic Outcome
Quantifying Pharmacometrics: Efavirenz example

Viral fitness

Drug concentration, fraction of $C_{\text{max}}$ vs. Time since $C_{\text{max}}$ (days)

- Shen et al. (Nat Med 2008)
- Sampah et al. (PNAS 2011)
- Jilek et al. (Nat Med 2012)
Quantifying Pharmacometrics: Efavirenz vs. Atazanavir/ritonavir

Drug concentration, fraction of $C_{\text{max}}$

Viral fitness

Time since $C_{\text{max}}$ (days)

Shen et al. (Nat Med 2008), Sampah et al. (PNAS 2011)
Jilek et al. (Nat Med 2012)
Pharmacometrics explain adherence-resistance relationships

**NNRTIs:** resistance at lower adherence

**Unboosted PIs:** resistance at higher adherence

**Boosted PIs:** low peak at intermediate adherence

Rosenbloom, Hill, Rabi et al. *(Nat Med 2012)*

cf. Maggiolo et al. *(HIV Clin Trials 2007)*

& Bangsberg et al. *(J Antimicrob Chemother 2004)*
Pharmacometrics predict virologic outcomes

Viral fitness

Viral dynamic model

Burst rate, Virus decay rate, Infection rate...

Infection rate depends on fitness

Viral load predictions
Pharmacometrics predict virologic outcomes

Viral fitness

Viral dynamic model

Burst rate, Virus decay rate, Infection rate...

Viral load predictions

Allows comparison across regimens!

Infection rate depends on fitness
Pharmacometrics predict virologic outcomes after treatment changes.

“NIMROD” program, Commenges & Thiebaut Group
Prague et al. (Biometrics 2012)
Prague et al. (Adv Drug Deliv Rev 2013)
Pharmacometrics + adherence predict virologic outcomes after treatment changes

“NIMROD” program, Commenges & Thiébaut Group
Prague et al. (Biometrics 2012)
Prague et al. (Adv Drug Deliv Rev 2013)
Pharmacometrics + MEMS
→ Viral fitness over time (illustrative)

Rosenbloom et al. *(Nat Med 2012)*
MACH14: 2,835 patients, 16,000 VL, 678,000 MEMS

* Requirements:
- 10 – 120 days between VL observation
- ≤ 3 consecutive days missing data
- Adherence between 20% and 110%
- ≥ 1 pill taken in 10 days before VL observation

12,985 inter-VL measurement periods

..907 starting suppressed (≤ 200 c/ml) w/o big data gaps*

... 119 with 3+ drug regimen data

- 86 / 907 rebound (9%)
- 14 / 119 rebound (12%)

www.mach14.med.ucla.edu
119 cases with ≥ 3 drugs

* Over inter-VL period up to 60 days

![Graph showing adherence and fitness levels](image-url)
119 cases with ≥ 3 drugs

Inhibitory factor (IF)

Adherence

Lower fitness

Higher fitness

Rebounded

Stays suppressed
119 cases with ≥ 3 drugs
IF is higher in suppressors

(Mann-Whitney U test)
119 cases with ≥ 3 drugs
A protective effect at IF > 8?

- IF > 8: 0 / 36 rebound
- IF ≤ 8: 14 / 83 rebound
  (Fisher exact test, p < 0.01)
IF may signal strong antiviral activity even when adherence is spotty.
Goals

• Use fitness from rich adherence data in viral dynamic models

• Test fitness for real-time guidance?
Thank you!

- **MACH14 Team**
  - Carol Golin
  - Honghu Liu
  - Bob Remien
  - Yan Wang
  - Ira Wilson

- **Harvard Program for Evolutionary Dynamics**
  - Alison Hill
  - Martin Nowak

- **Johns Hopkins**
  - Ali Rabi
  - Bob Siliciano

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  - Harvard Organismic & Evolutionary Biology
  - NIH
  - HHMI
MACH14 regimen overview: 119 cases with ≥ 3 drugs

Count

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<th>Regimen</th>
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<th>Continued suppression</th>
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Rebounded
Continued suppression
A protective effect at IF > 8?
... for all 907 with full/partial regimens

- IF > 8: 0 / 39 rebound
- IF ≤ 8: 86 / 868 rebound

(Fisher exact test, p = 0.04)
IF is “common currency” that describes many regimens.
Above 70% adherence, only IF matters

(Mann-Whitney U test)
IF may signal strong antiviral activity even when adherence is spotty

Daily IF

EFV 600mg (q.d)
AZT 300mg + 3TC 150mg (b.i.d.)

VL < 50 c/ml
VL = 121 c/ml

28-day average = 8.6
18 / 28 = 64%
39 / 56 = 70%