8th International Conference on HIV TREATMENT AND PREVENTION ADHERENCE

Predicting treatment outcomes using rich adherence data & antiretroviral pharmacometrics

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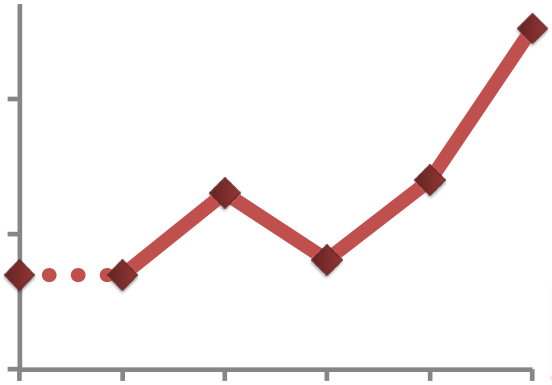
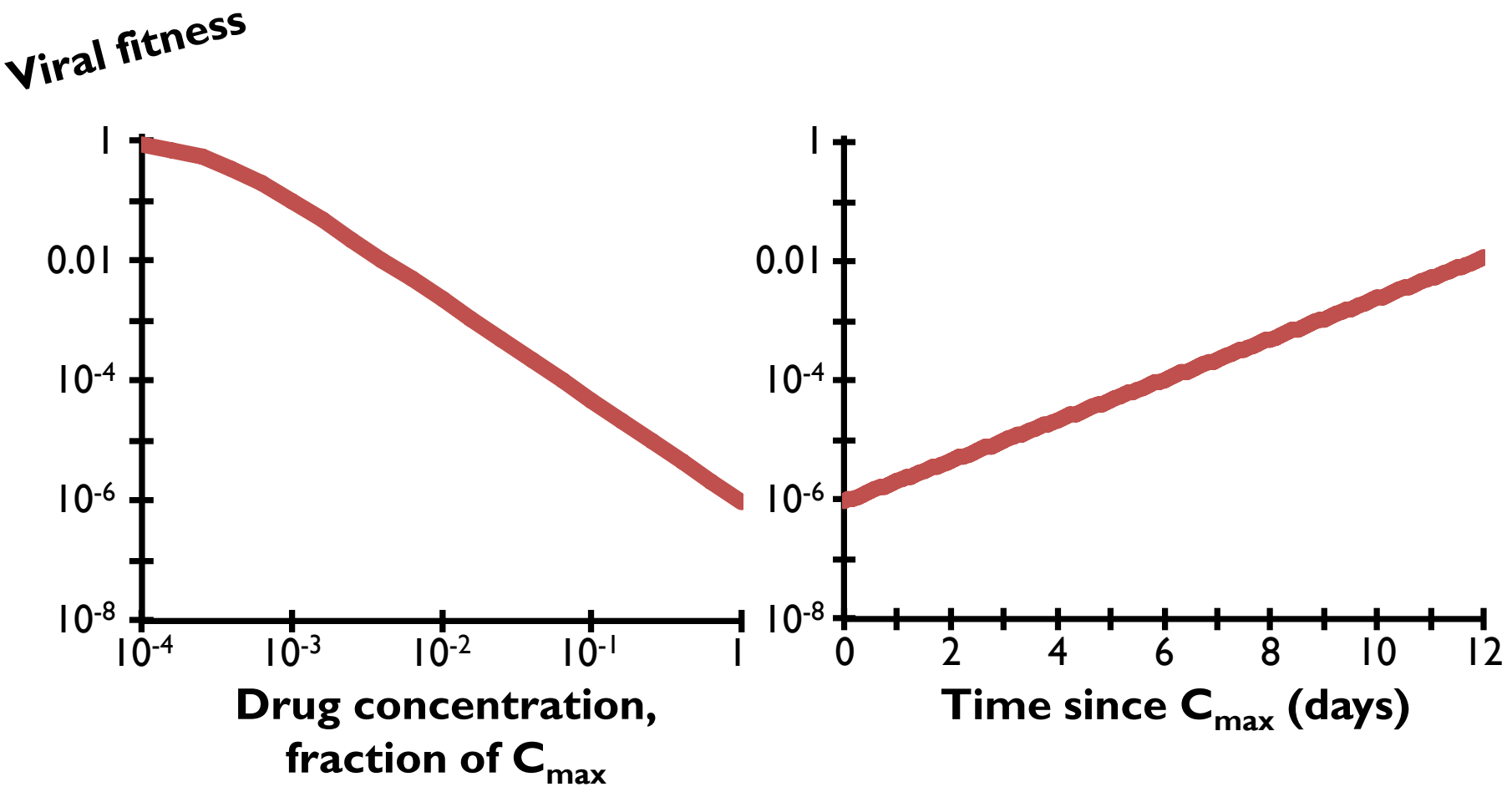
Regimen & Adherence

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

Virologic Outcome

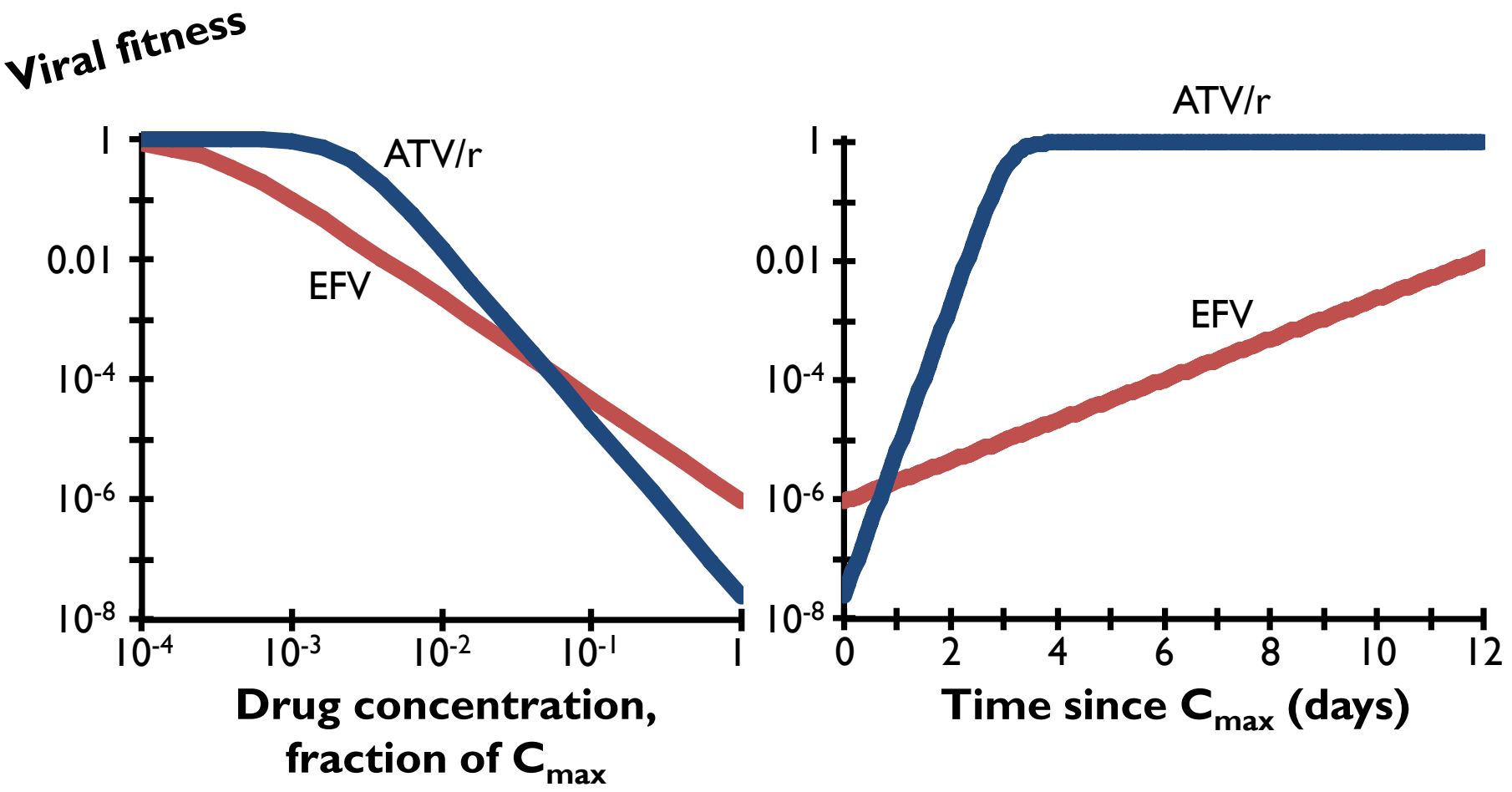


Quantifying Pharmacometrics: Efavirenz example



Shen et al. (*Nat Med* 2008), Sampah et al. (*PNAS* 2011)
Jilek et al. (*Nat Med* 2012)

Quantifying Pharmacometrics: Efavirenz vs. Atazanavir/ritonavir



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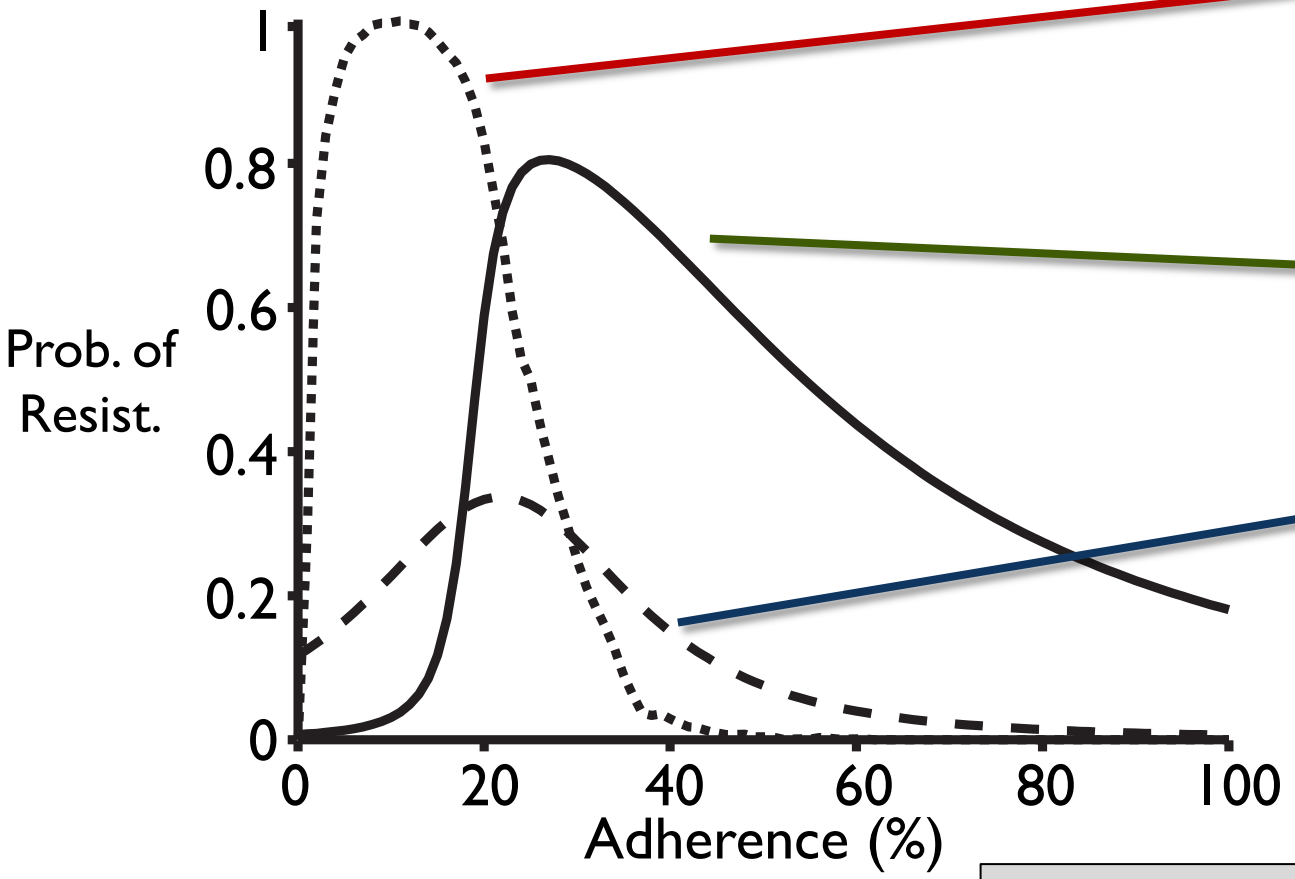
Pharmacometrics explain adherence-resistance relationships



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)

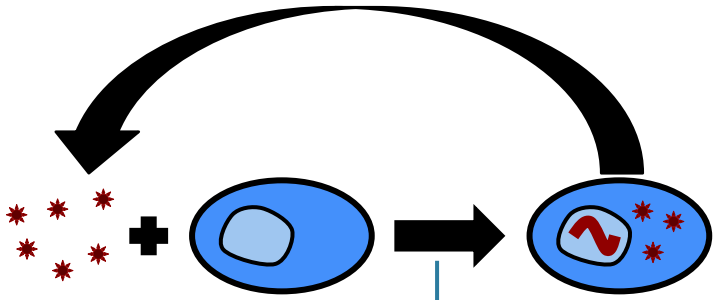
Pharmacometrics predict virologic outcomes

Viral fitness

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

Viral dynamic model

Viral load predictions



Infection rate depends on fitness

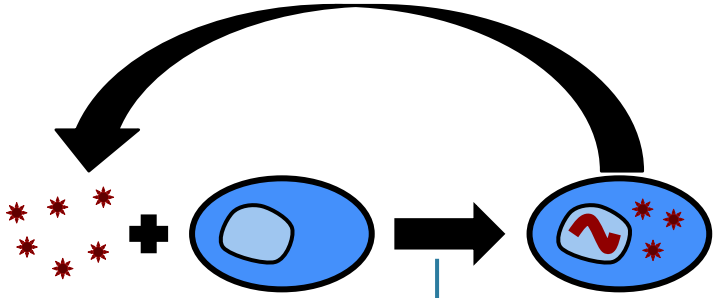
Pharmacometrics predict virologic outcomes

Viral fitness

Allows comparison across regimens!

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

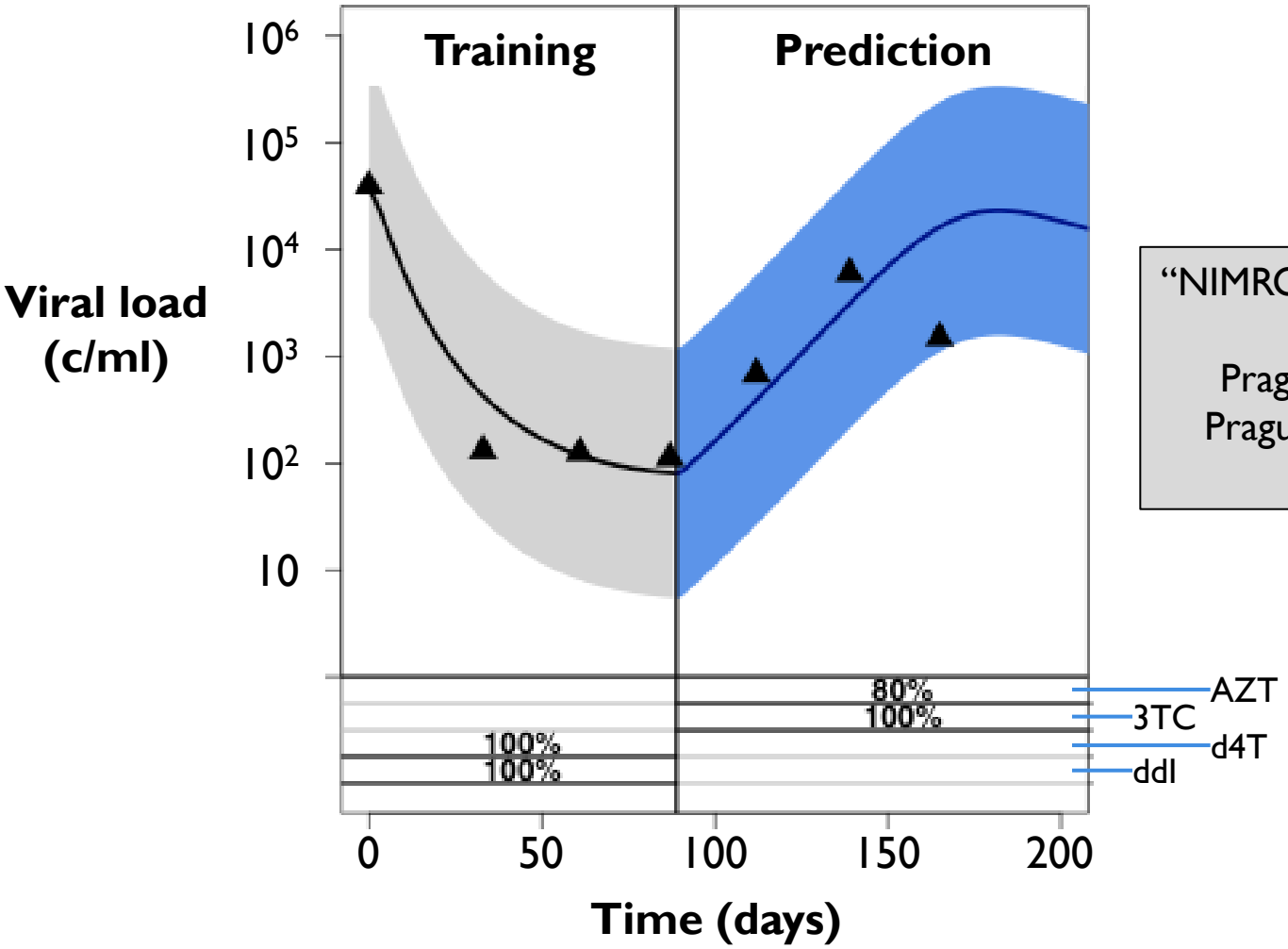
Viral dynamic model



Infection rate depends on fitness

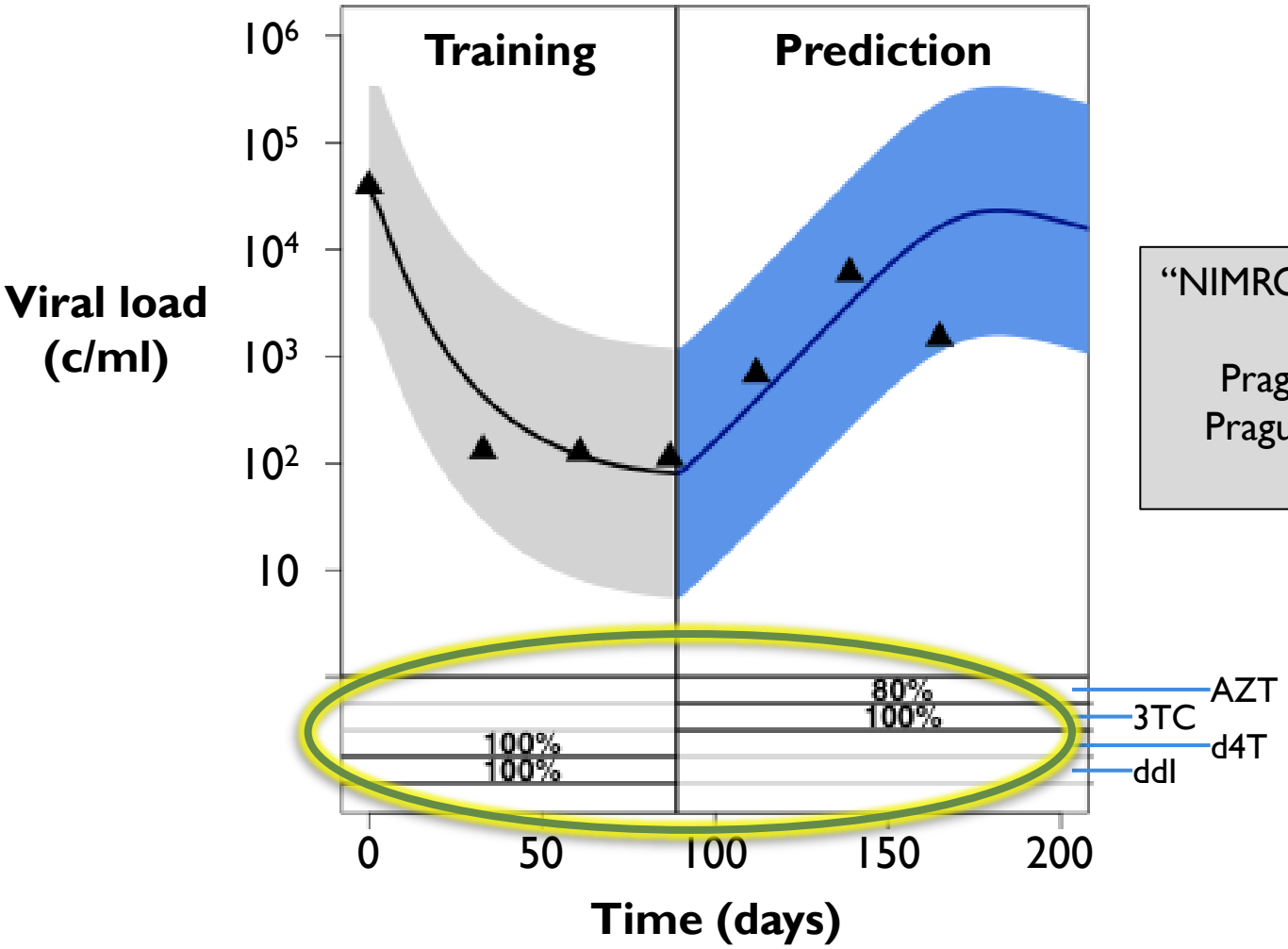
Viral load predictions

Pharmacometrics 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 + adherence predict virologic outcomes after treatment changes



"NIMROD" program, Commenges & Thiébaut Group
Prague et al. (*Biometrics* 2012)
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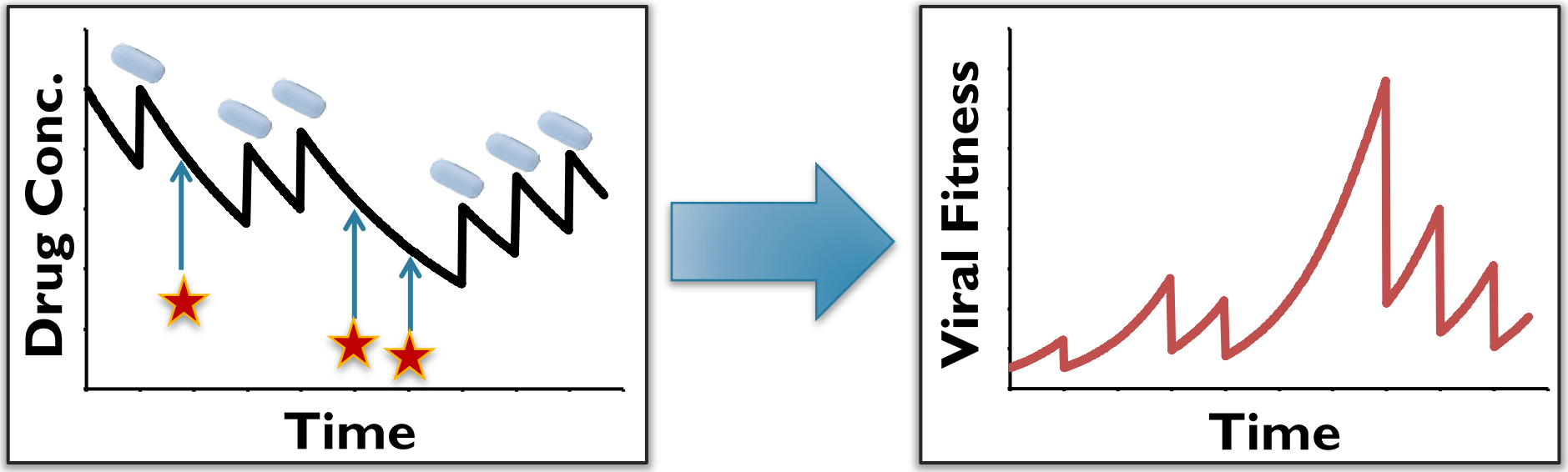
Pharmacometrics + MEMS

→ **Viral fitness over time** (illustrative)



Rosenbloom et al. (*Nat Med* 2012)

MACH14:
2,835 patients, 16,000 VL, 678,000 MEMS

12,985 *inter-VL measurement periods*

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

... 119 with *3+ drug regimen data*

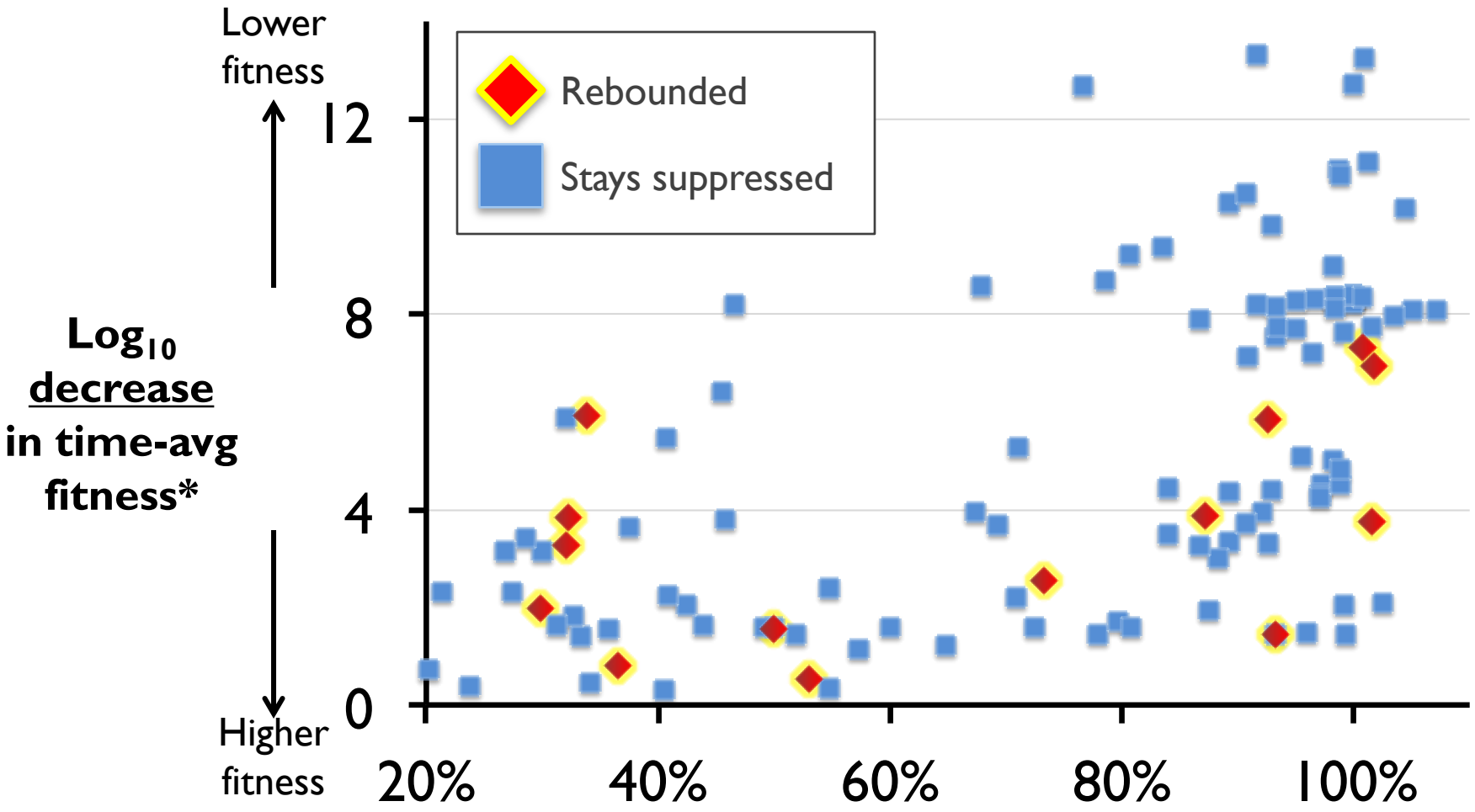
- **86 / 907 rebound (9%)**
- **14 / 119 rebound (12%)**

www.mach14.med.ucla.edu

*** Requirements:**

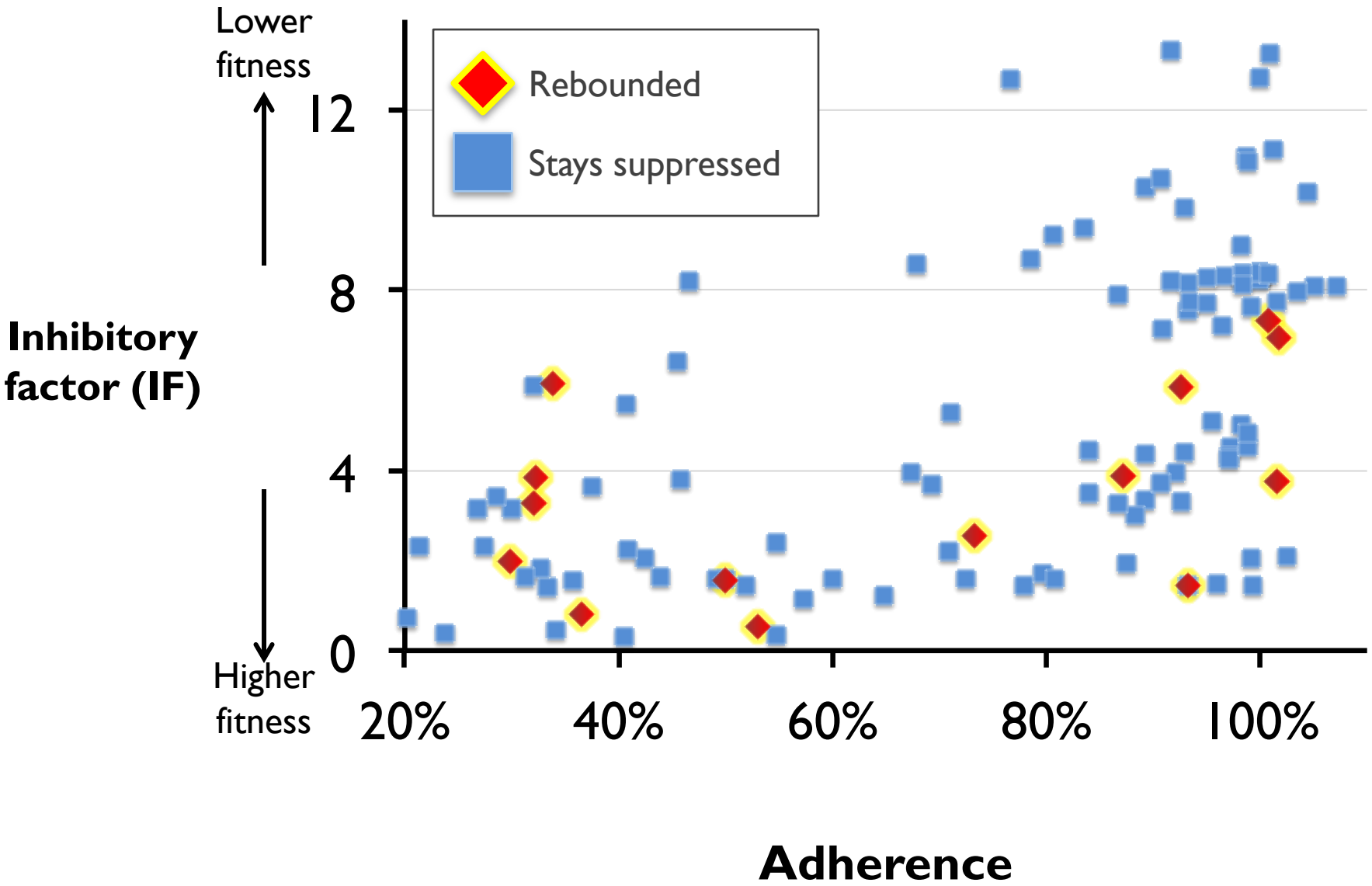
- 10 – 120 days btwn. VL observation
- ≤ 3 consecutive days missing data
- Adherence btwn. 20% and 110%
- ≥ 1 pill taken in 10 days before VL observation

119 cases with ≥ 3 drugs

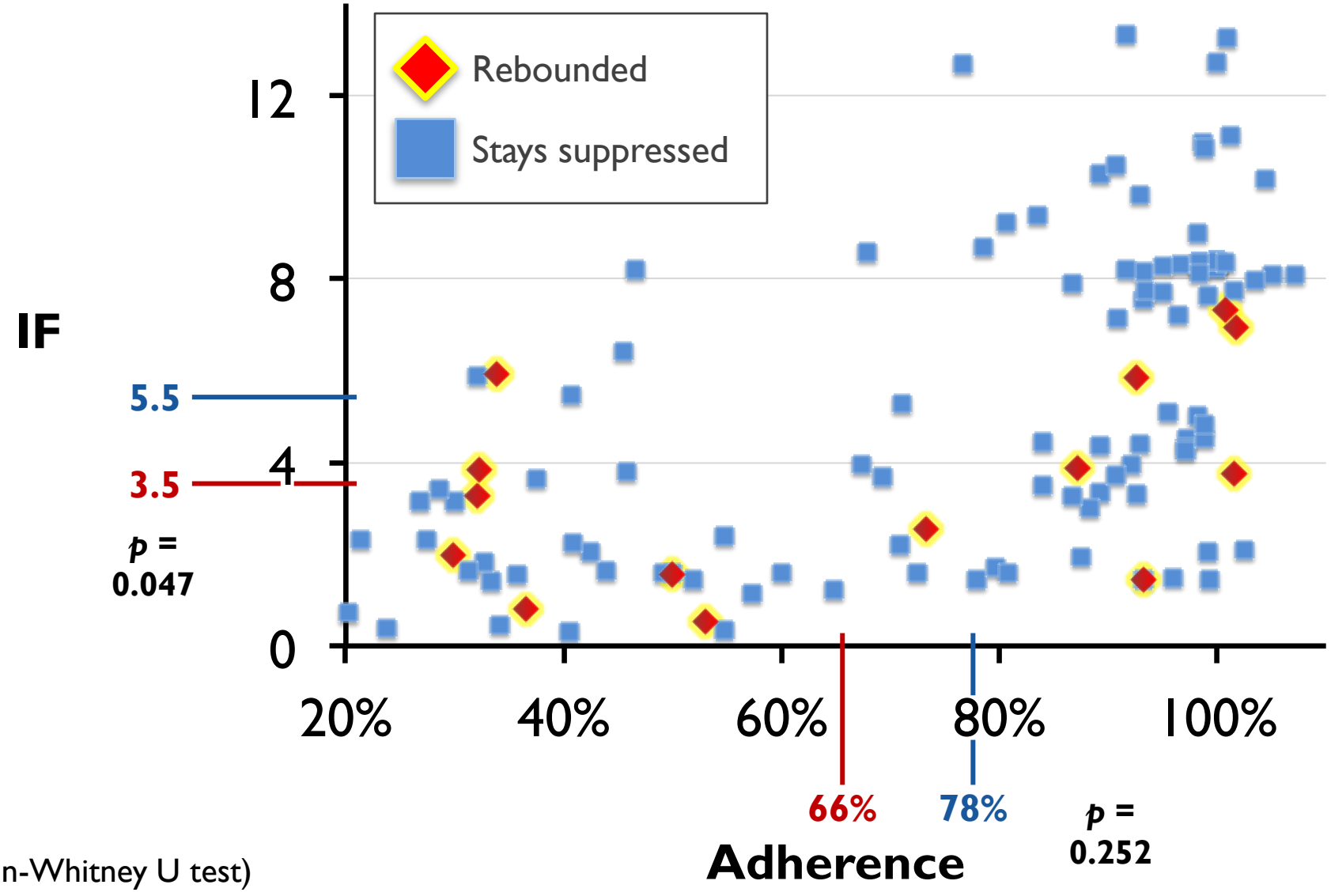


* Over inter-VL period up to 60 days

119 cases with ≥ 3 drugs



119 cases with ≥ 3 drugs
IF is higher in suppressors

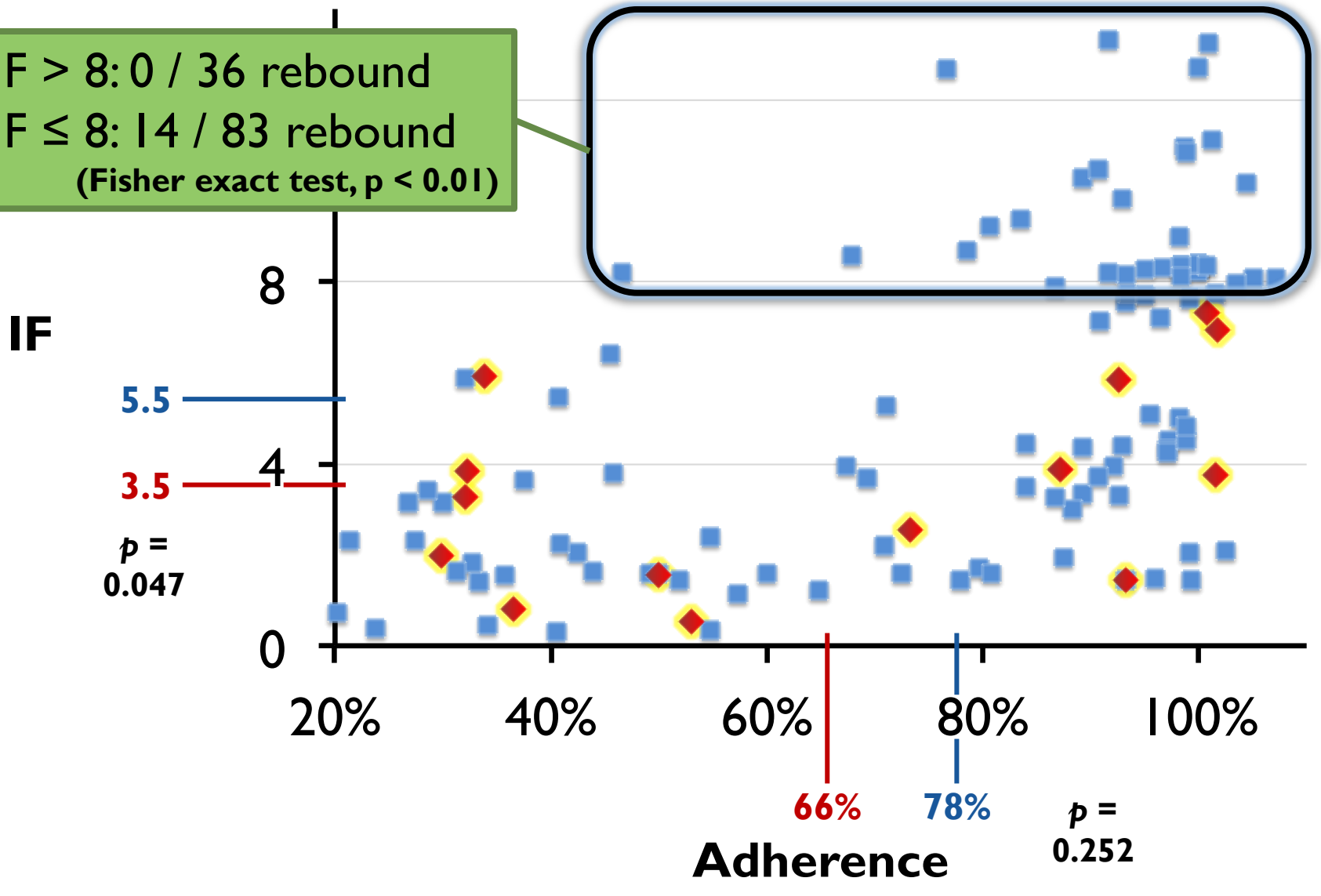


(Mann-Whitney U test)

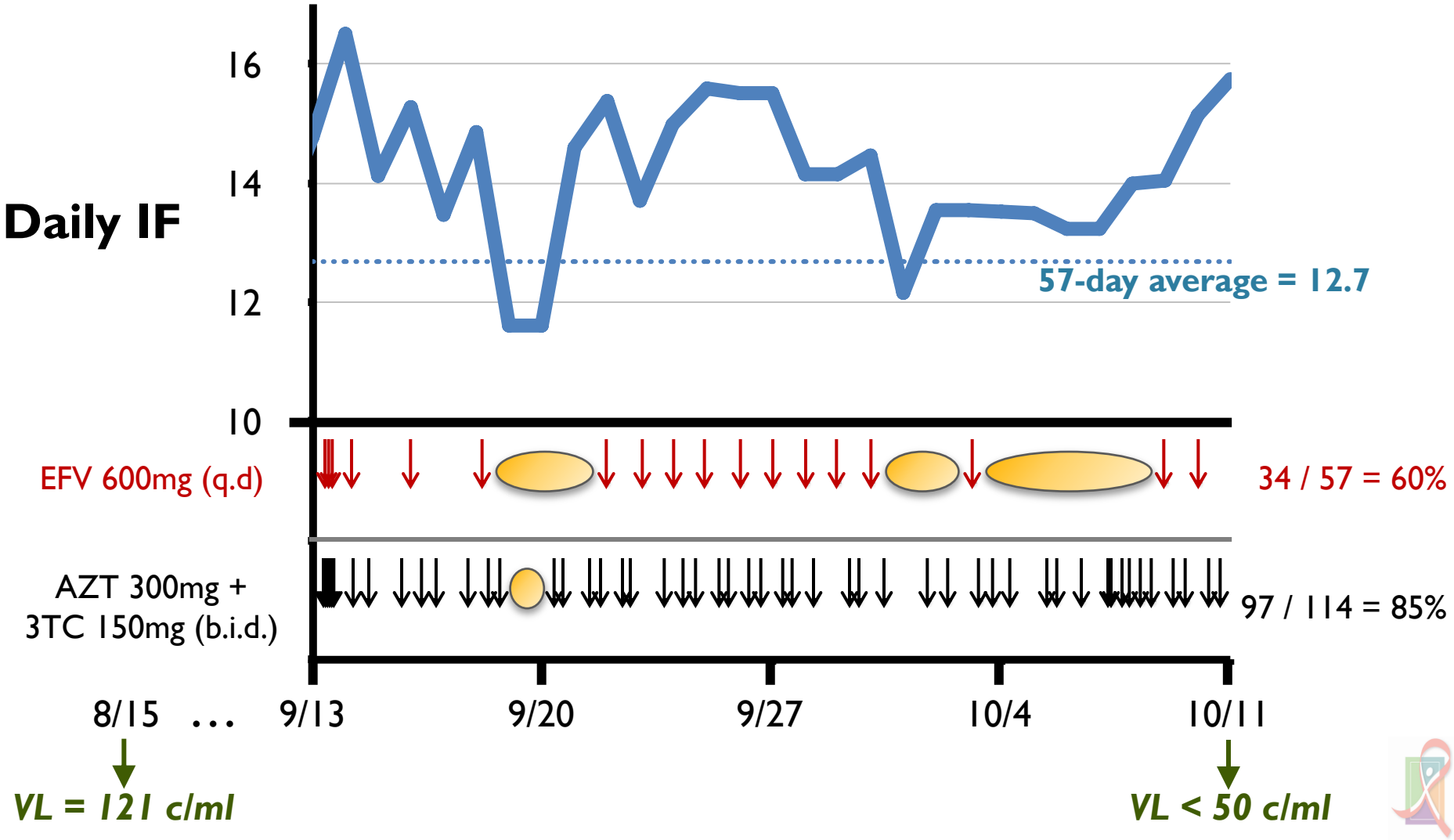
119 cases with ≥ 3 drugs
A protective effect at IF > 8?

- 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

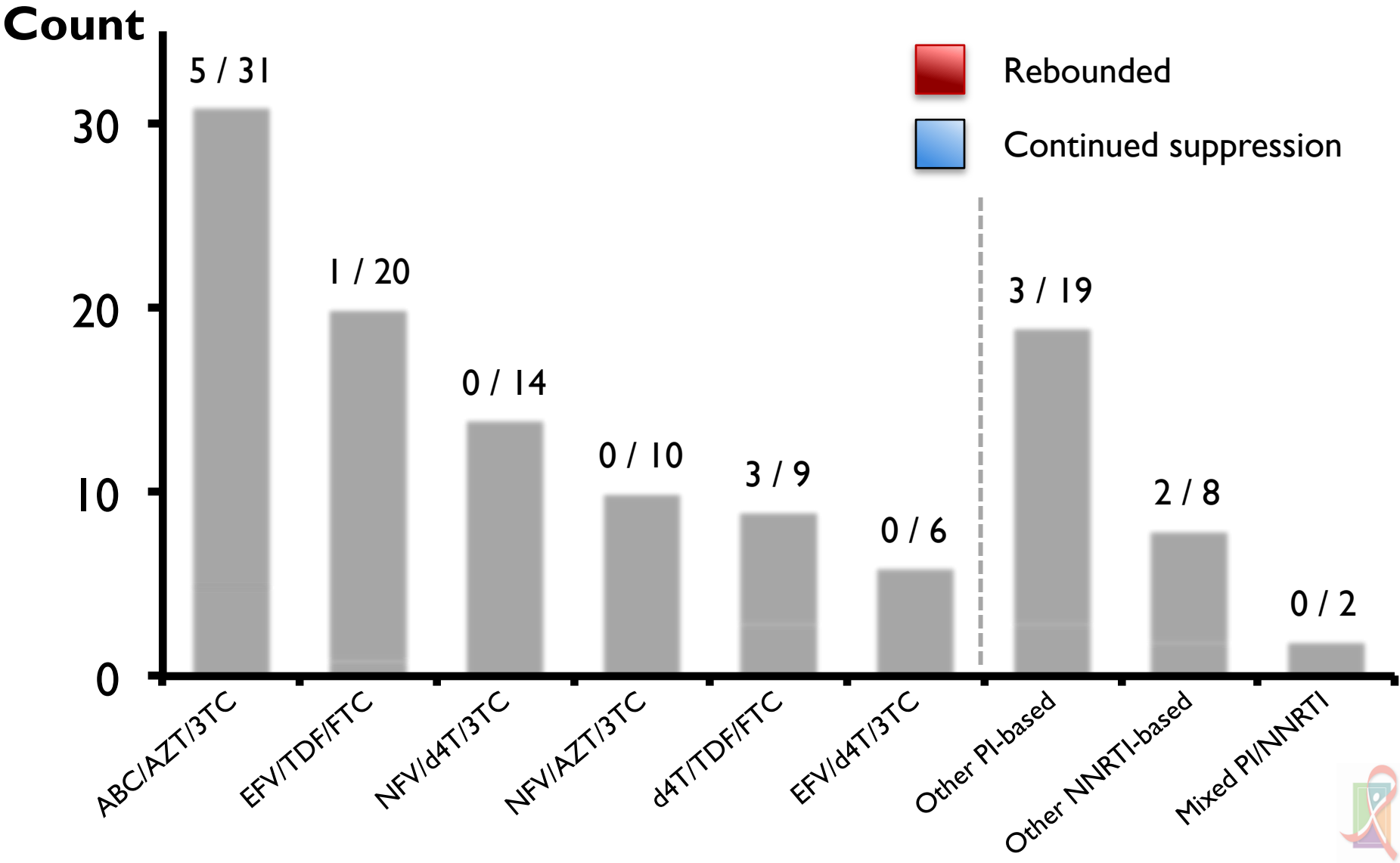
- Use fitness from rich adherence data in viral dynamic models
- Test fitness for real-time guidance?

Thank you!

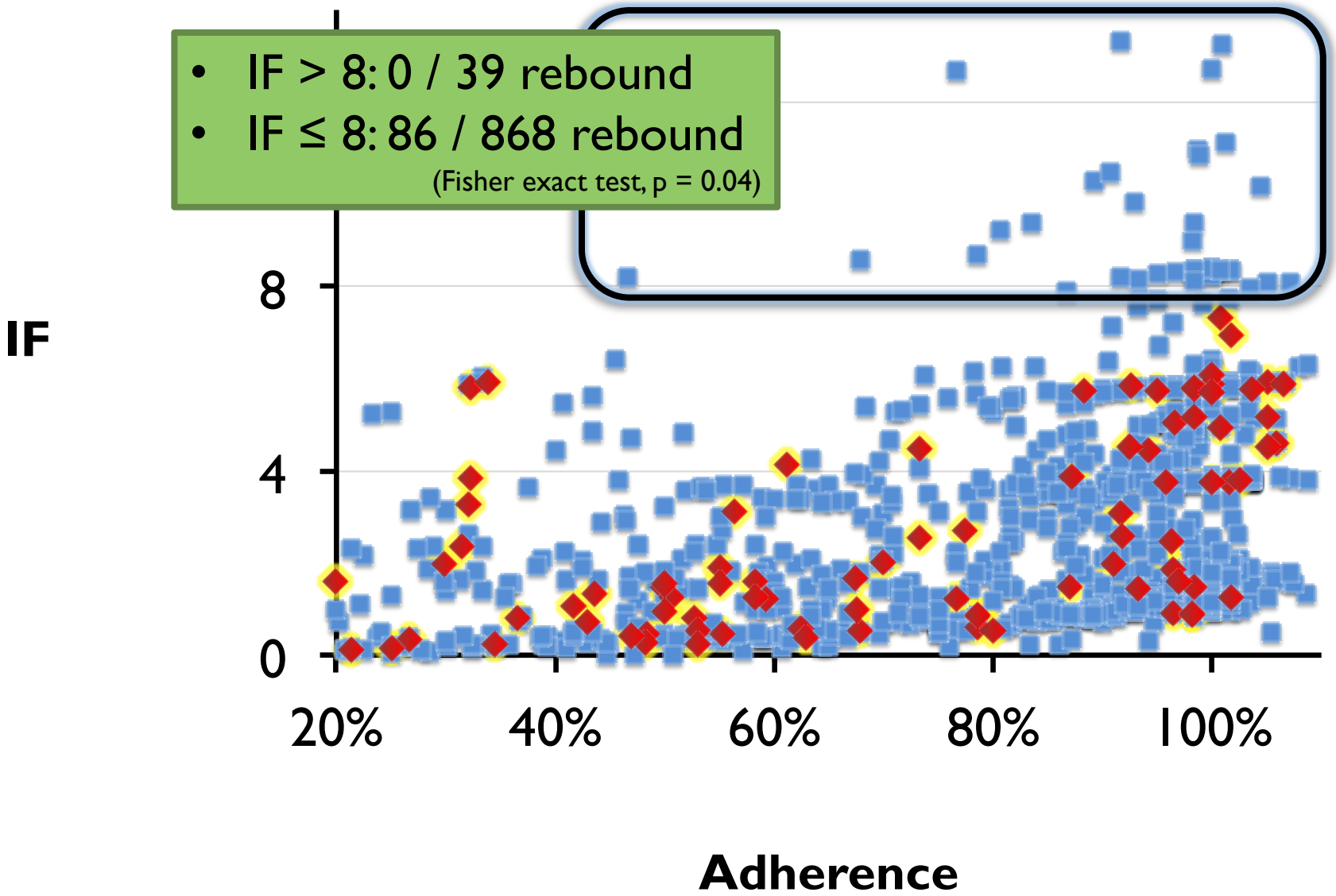
- **MACH14 Team**
  - Carol Golin
  - Honghu Liu
  - Bob Remien
  - Yan Wang
  - Ira Wilson
- **Harvard Program for Evolutionary Dynamics**
  - Alison Hill
  - Martin Nowak
- **Johns Hopkins**
  - Ali Rabi
  - Bob Siliciano

- **Financial support:**
  - Harvard Organismic & Evolutionary Biology
  - NIH
  - HHMI

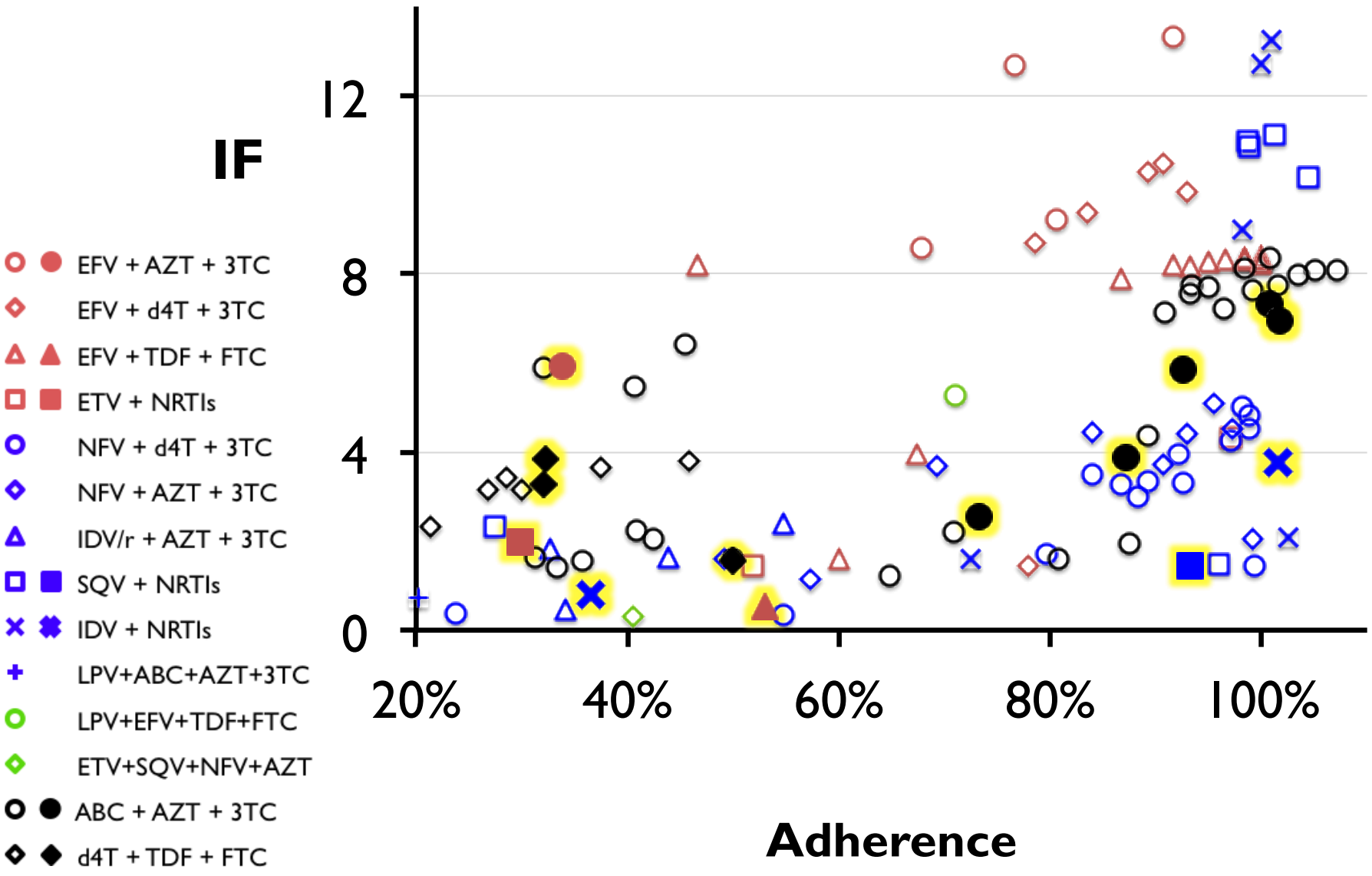
MACH14 regimen overview: 119 cases with ≥ 3 drugs



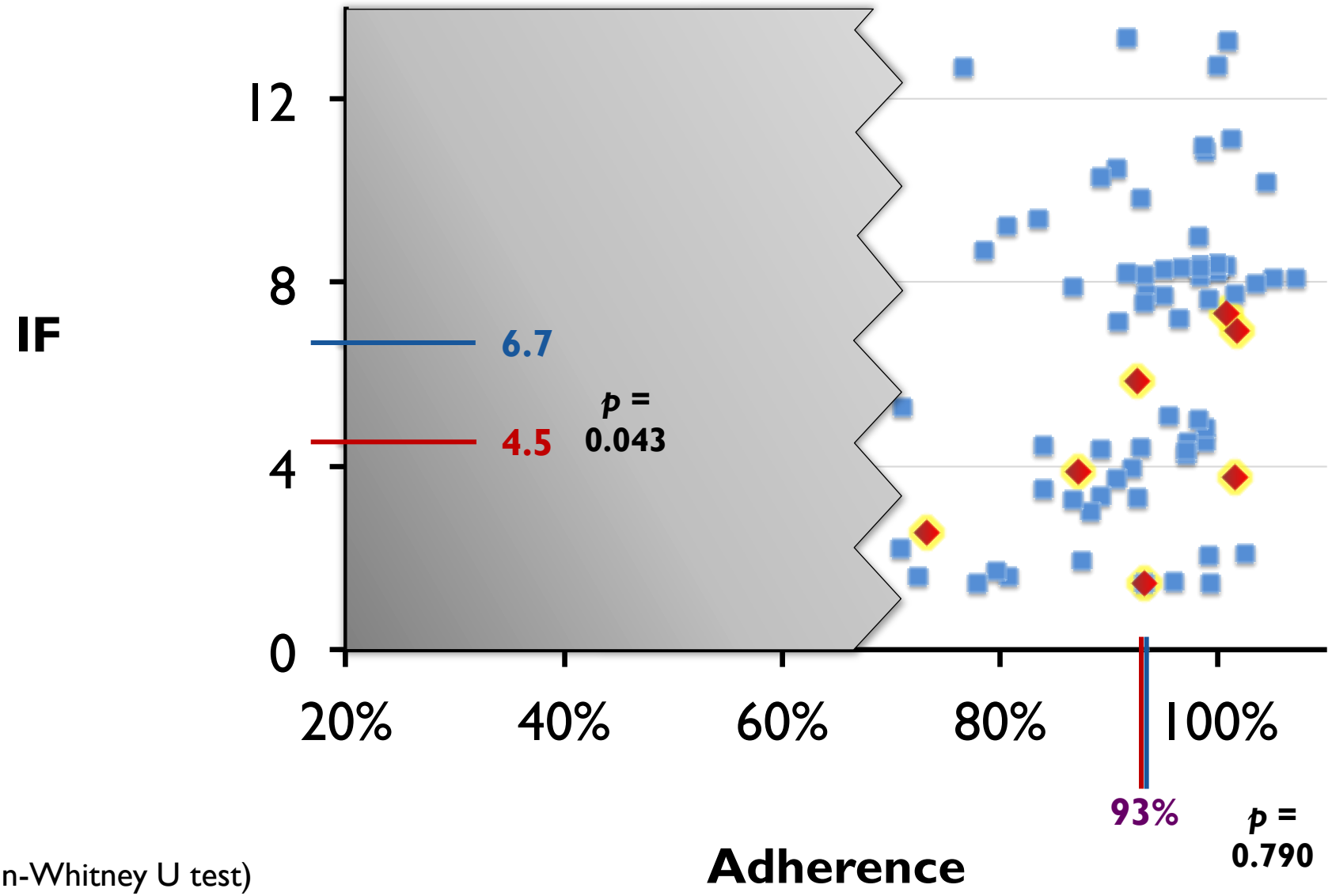
A protective effect at IF > 8?
... for all 907 with full/partial regimens



IF is "common currency" that describes many regimens



Above 70% adherence, only IF matters



(Mann-Whitney U test)

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