

Dose-timing errors do not impact viral rebound among HIV-RNA suppressed patients

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June 4, 2013

8th International Conference on HIV
Treatment and Prevention Adherence

Miami, Florida



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Background

- Patterns of adherence are important
- Consecutive missed doses have an impact on suppression
- To date, there has been limited exploration of how the timing of doses impact viral suppression
- Timing of doses = early and late doses



Objectives

1. To capture dose-timing errors (DTE) using electronic monitoring data
2. To determine the impact of DTE on viral rebound, beyond the effect of dose adherence.



Primary challenges in the measurement of dose-timing errors

1. When does a late dose become a missed dose?
2. How to summarize measures of DTE over longer intervals of time?

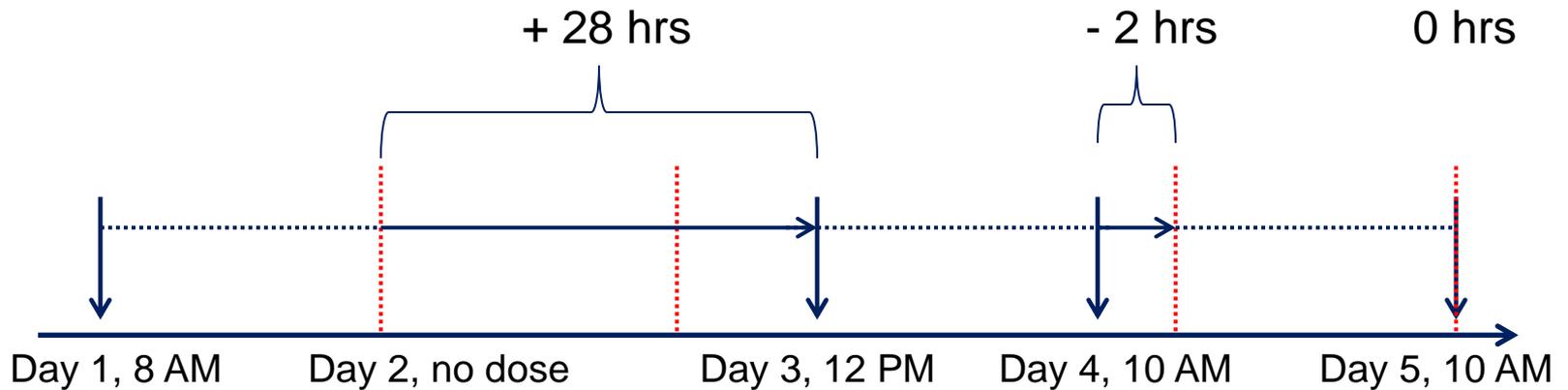


Dose-timing error measures

- Measures of DTE were created by summarizing MEMS data in the 4 weeks prior to HIV RNA measures.
- DTE measures were defined as:
 - Net timing error: summation of the differences between observed and expected dosing time.
 - Mean net timing error: average of the summed differences between the observed and expected dosing time.
 - Expected dose time = + 24 hours for 1/day, + 12 hours for 2/day, and + 8 hours for 3/day

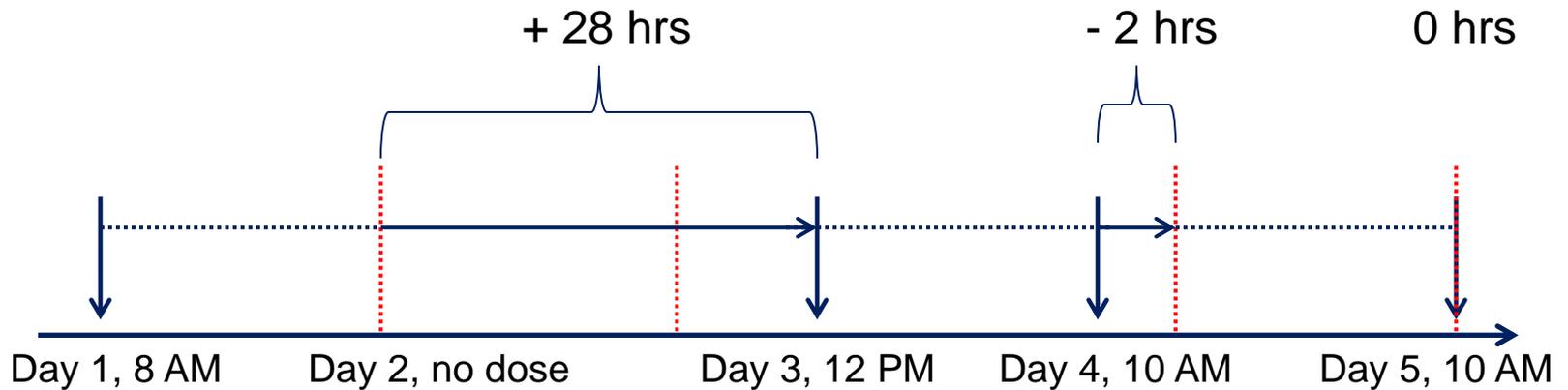


Contrasting two approaches

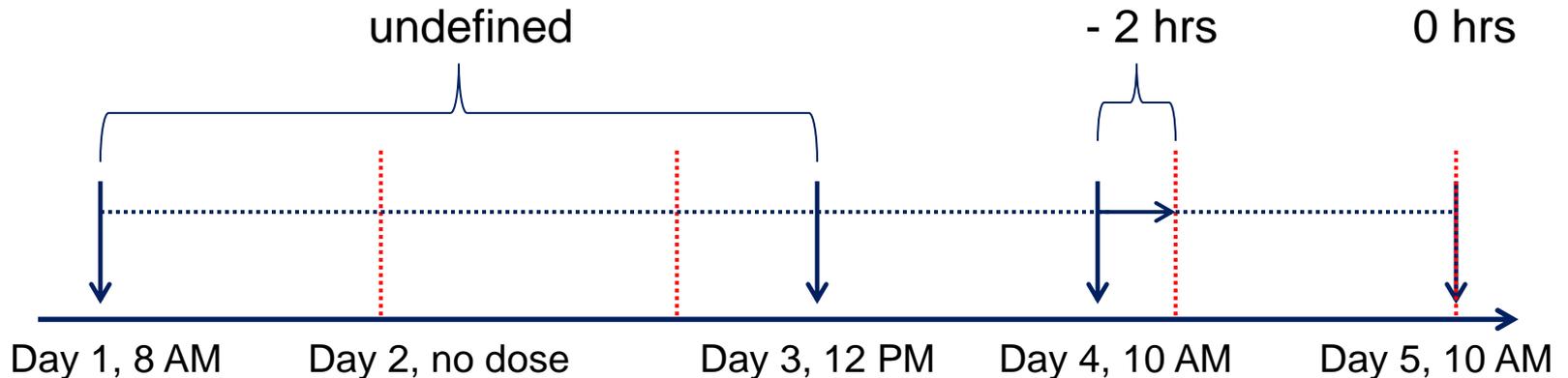


Net timing error: $+28 - 2 + 0 = 26$ hrs Mean net timing error: $(+28 - 2 + 0)/3 = 8.7$ hrs

Contrasting two approaches



Net timing error: $+28 - 2 + 0 = \mathbf{26 \text{ hrs}}$ Mean net timing error: $(+28 - 2 + 0)/3 = \mathbf{8.7 \text{ hrs}}$

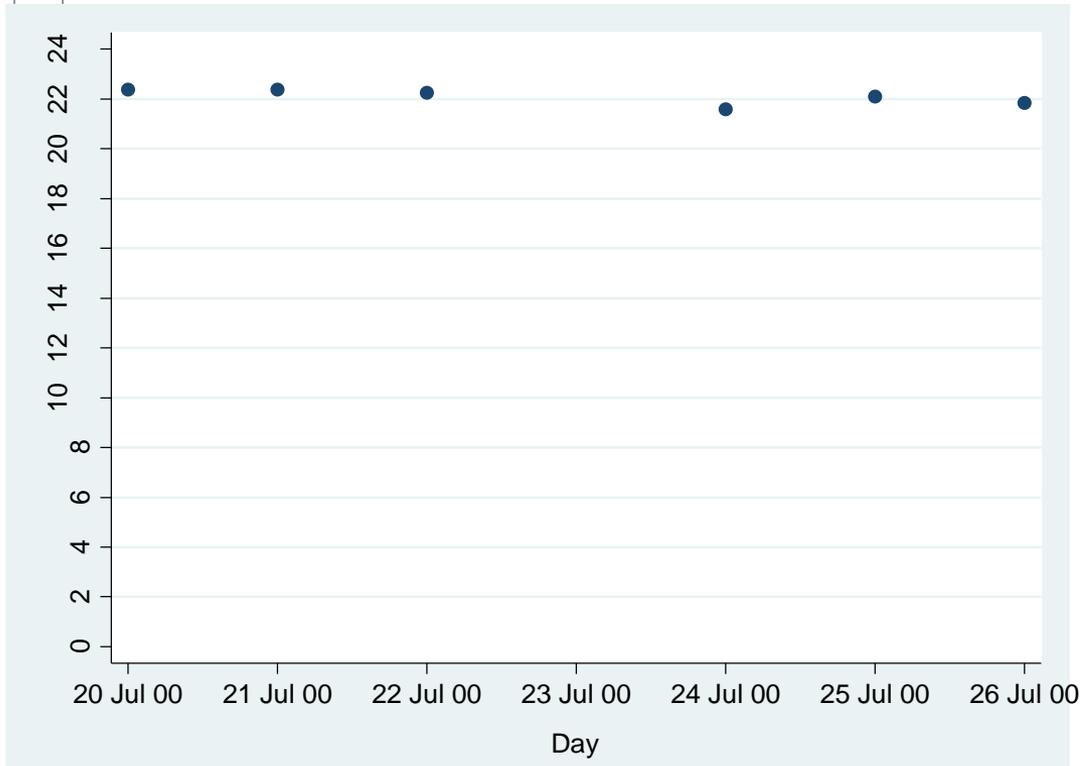


Net timing error: $-2 + 0 = \mathbf{-2 \text{ hrs}}$ Mean net timing error: $(-2 + 0)/2 = \mathbf{-1 \text{ hr}}$

Assumptions

- Doses that occurred after 1.5 times the expected interval = missed doses
- Doses that occurred at or before 1.5 times the expected interval = late doses
 - 1/day = 36 hours
 - 2/day = 18 hours
 - 3/day = 12 hours





Measures

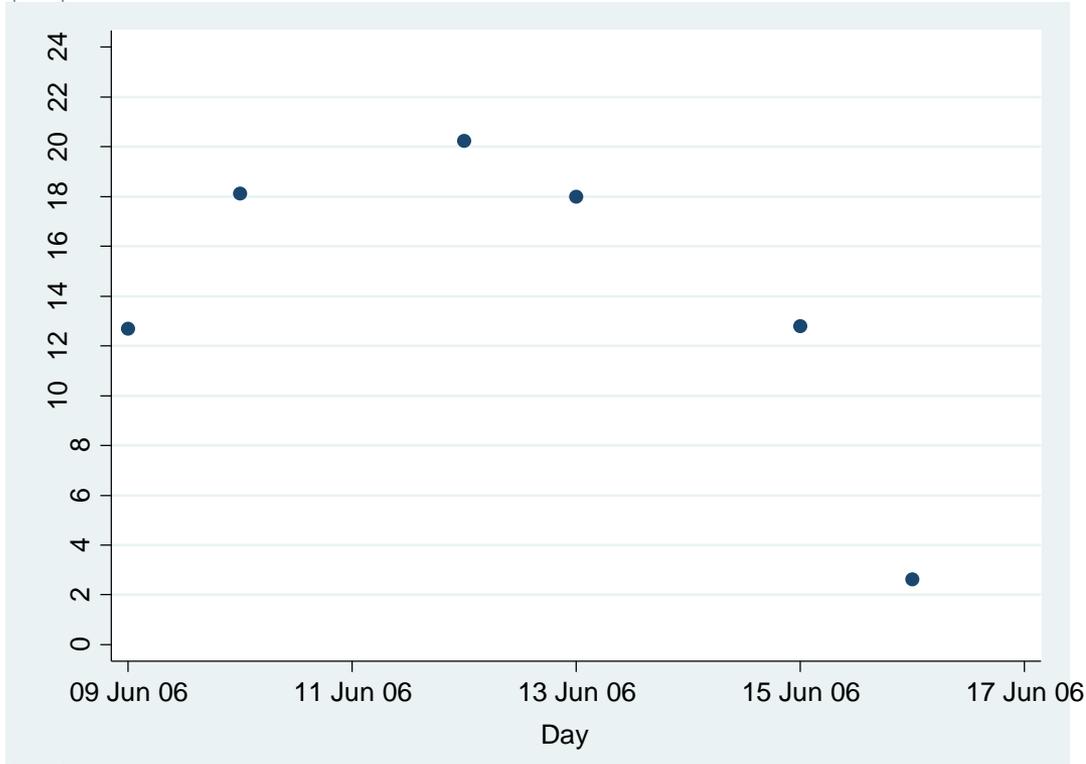
Average Adherence = $6/7 = 86\%$

Net timing error = **1.2 hours**

Mean net timing error = **0.3 hours**

Missed doses = 1 dose





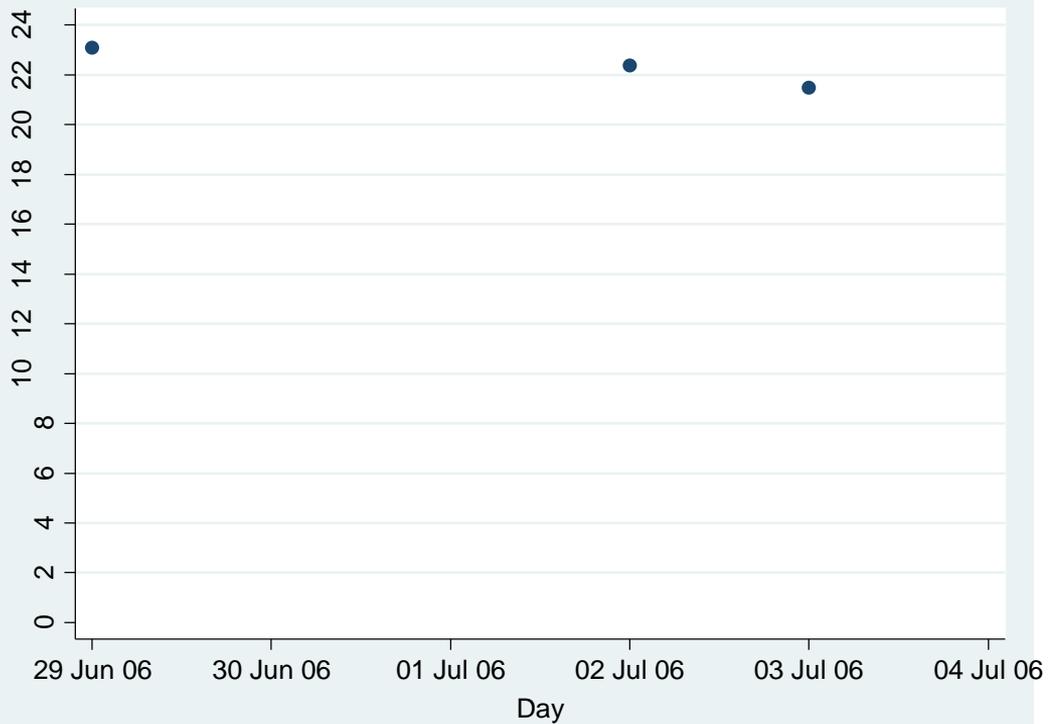
Measures

Average Adherence = $6/7 = 86\%$

Net timing error = **-7 hours**

Mean timing error = **-2.3 hours**

Missed doses = 2 doses



Measures

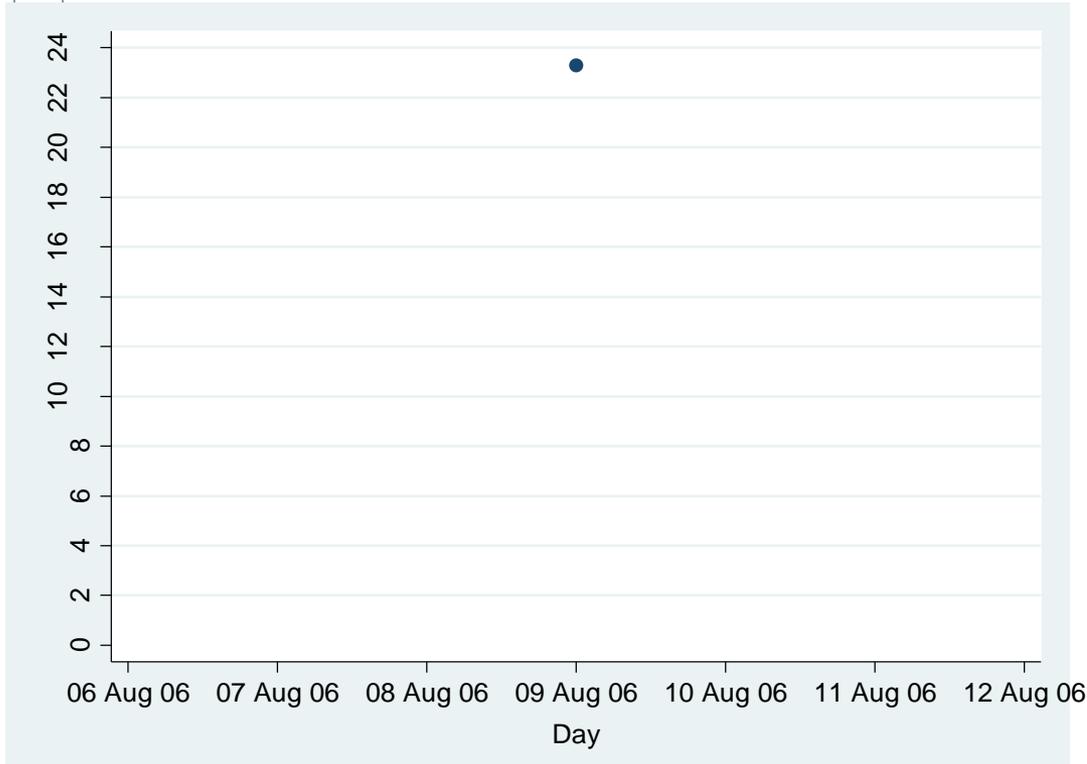
Average Adherence = $3/7 = 43\%$

Net timing error = **-0.9 hours**

Mean net timing error = **-0.9 hours**

Missed doses = 4 doses





Measures

Average Adherence = $1/7 = 14\%$

Net timing error = **undefined**

Mean net timing error = **undefined**

Missed doses = 6 doses



Assumptions, cont'd

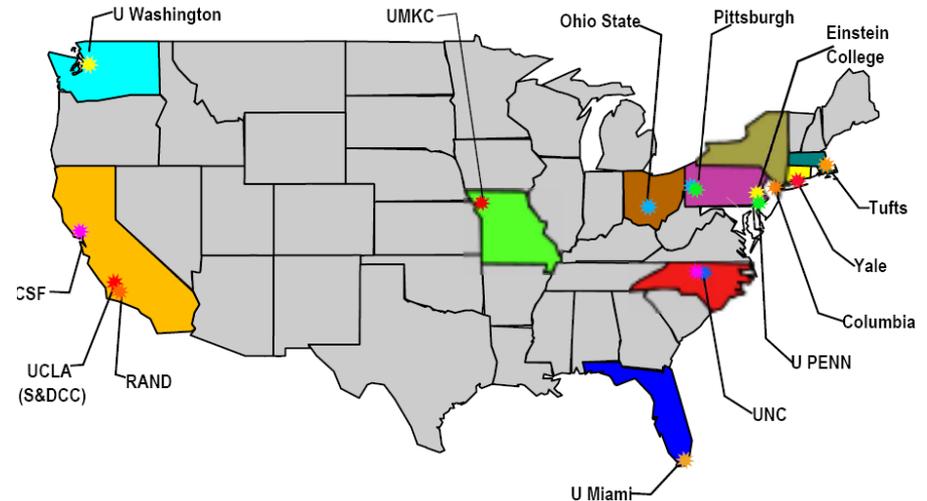
- Timing of doses cannot be measured unless there are enough doses within the interval.
 - Measurement of dose-timing was restricted to periods with at least 3 doses.



MACH-14 Study

Multi-Site Adherence Collaboration in HIV

- 16 NIH-funded HIV adherence studies from 14 institutions across 12 states were conducted between 1997 and 2009
- Required: 1) a longitudinal study design; 2) MEMS adherence data; 3) viral load and clinical outcomes; and 4) psychosocial and behavioral measures
- 2,860 patients infected with HIV, followed for a mean of 18 months



Methods: Study Sample

- 580 individuals contributed 2,243 person-periods (28-days of adherence data followed by an HIV RNA measure)
- Included:
 - 1x, 2x, 3x daily dosing regimens
 - Continuous MEMS monitoring during follow-up
 - ≥ 4 weeks follow-up preceding HIV RNA measures
 - <5 doses/day
 - Suppressed HIV RNA (below 400 copies/mL)



Methods

- Impact of DTE on first viral rebound (≥ 400 copies/mL) examined using random effects models
- Compared AUC curves
 - Average adherence
 - Average adherence + mean net timing error
 - Average adherence + net timing error

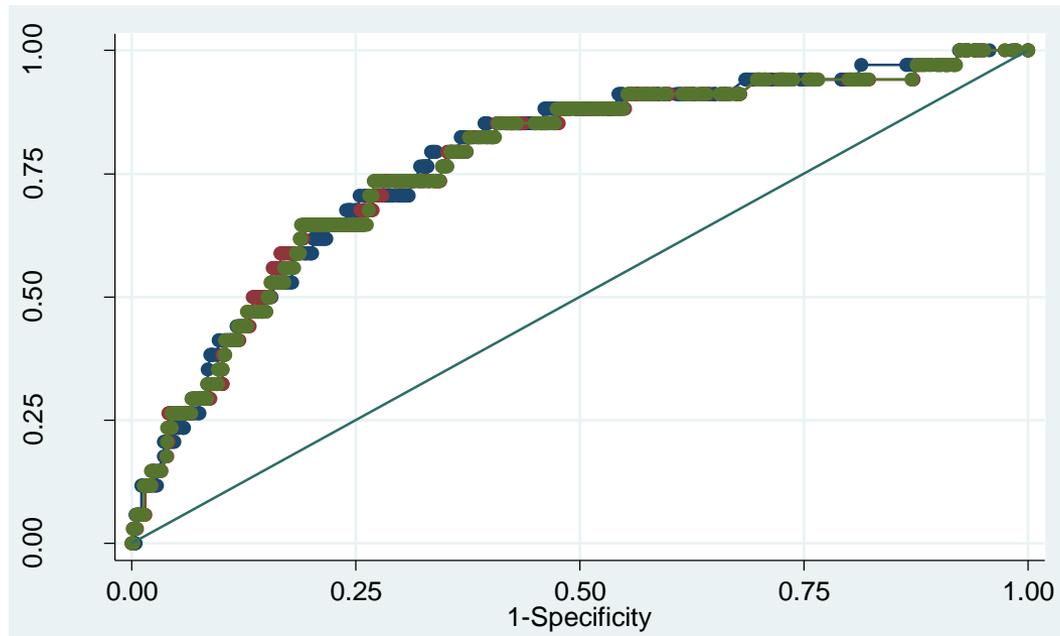


Results: study sample

- 580 participants
- 71% male
- 42% African-American
- 36% treatment-naïve at baseline
- Mean age: 40 years
- Average monthly adherence: 63% (SD =34)
- 5% of the person-periods had viral rebound



Results



No difference in AUC when either DTE measure is added to average adherence ($p=0.59$)

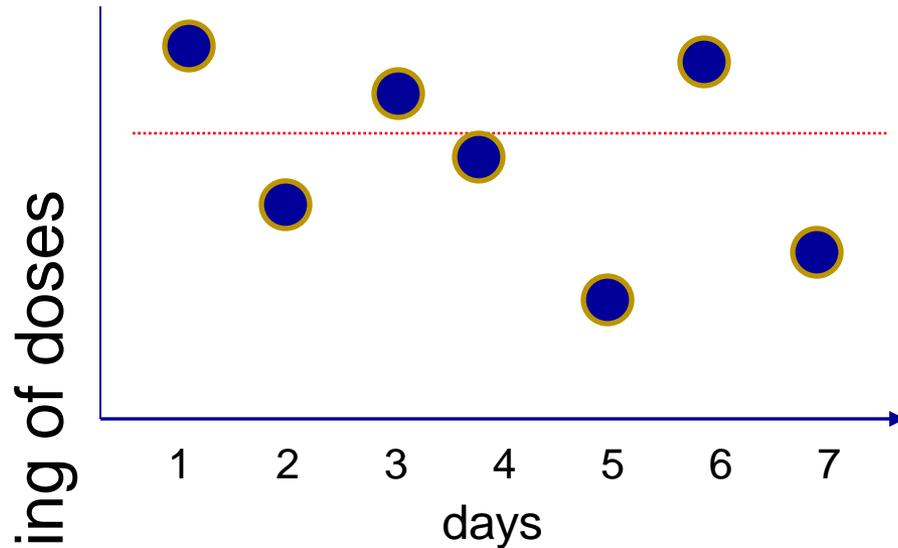


Summary

- Dose-timing does not seem to be a useful concept unless patients exceed a threshold of adherence
- Dose-timing is not measurable if there are not enough doses to assess timing
- For those with poor adherence, patterns of dose-taking rather than dose-timing, are more important
- For those with good adherence, dose-timing does not have an impact on viral rebound

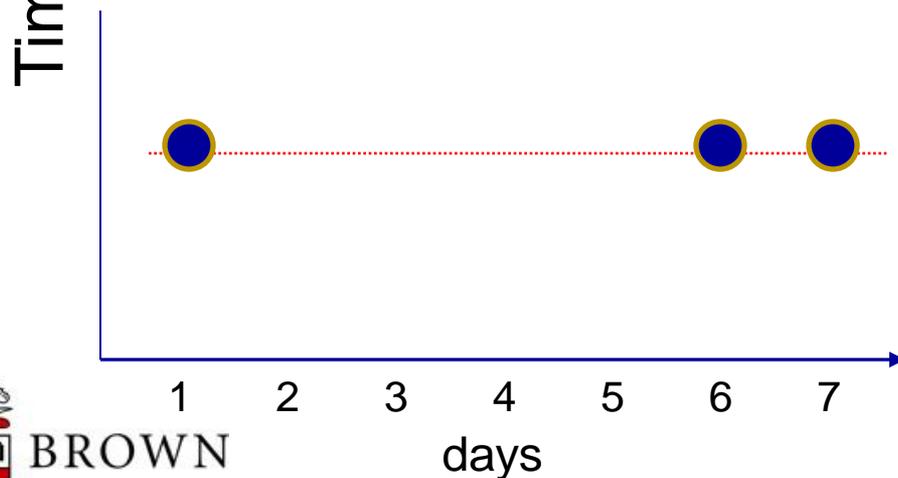


Examine two dimensions: doses and timing



Frequent doses, inconsistent timing

vs.



Infrequent doses, consistent timing



Limitations

- Limited power due to few events (e.g., viral rebound) among those with good adherence
 - Unable to examine more subtle differences in timing among those with good adherence
- Examined dose-timing aggregated across treatment regimens
 - Future work to explore differences by regimen
- Measurement issues related to electronic monitoring devices
 - Use of device = taking pills?
 - Not using device = not taking pills?



Implications

- Anchoring schedule around stable dose times may be helpful for patients and logical for providers.
- However, patients who do not have stable schedules, and those who end up with intermittent late or early doses, are unlikely to have to worry about these timing issues (...as long as the dose is taken!)
- Clinical efforts should focus on preventing interruptions in medication-taking

