Nonparametric tests for two group comparisons of dependent observations obtained at varying time points with application to RNA viral load decline

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Outline

- Motivation
- Two new tests
- Example data / Simulations
- Asymptotics
- Comparison to other tests
- Summary

Motivation

- AIEDRP
  - Acute HIV Infection and Early Disease Research Program
- Research question:
  - RNA decline slower with transmitted drug resistance?
- Study group: Tx naïve HIV+ patients who start ARV

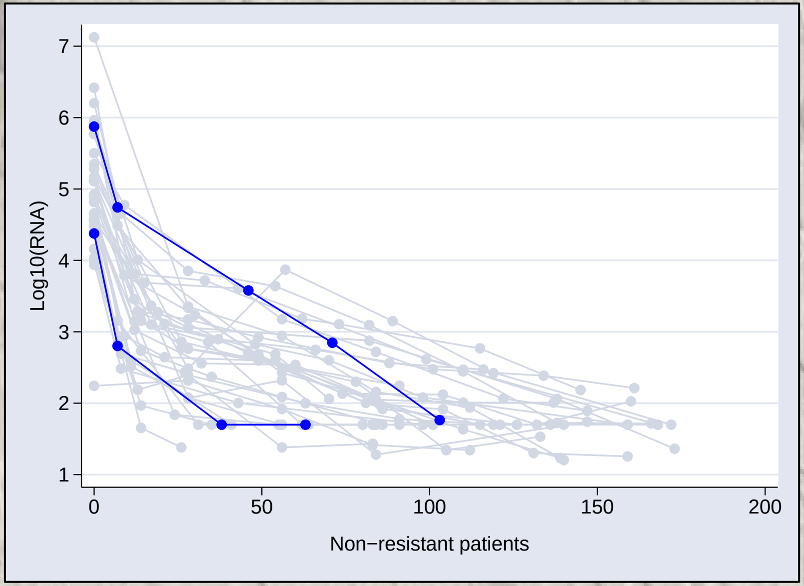
Motivation

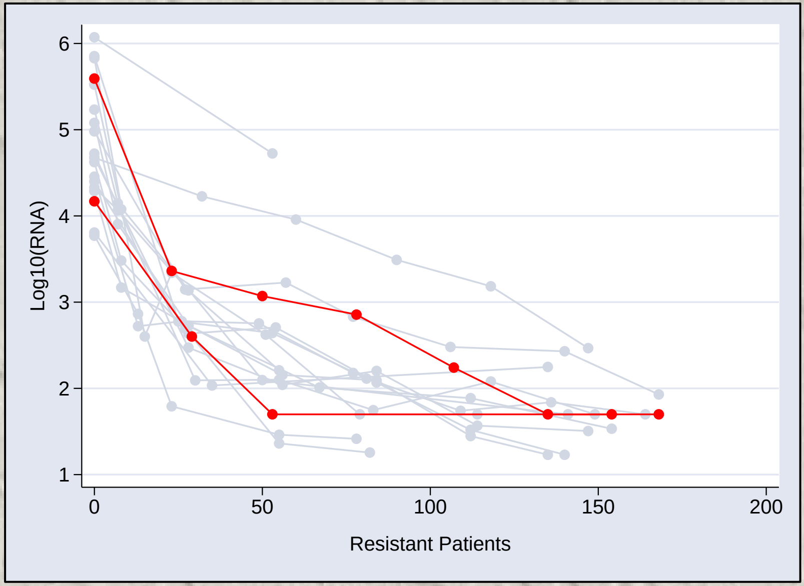
- 15-20 drugs available, 3 drug classes
- Regimen of 3-4 drugs
- Virus mutating
- Resistance to drug(s), drug classes
- Transmitted to uninfected individual
- Newly infected has drug resistant virus

- Outcome: Decline in RNA viral load over time
  Viral load can be censored, above and below
- Groups: Resistant vs Sensitive

Motivation

- **AIEDRP Data, Los Angeles and San Diego**





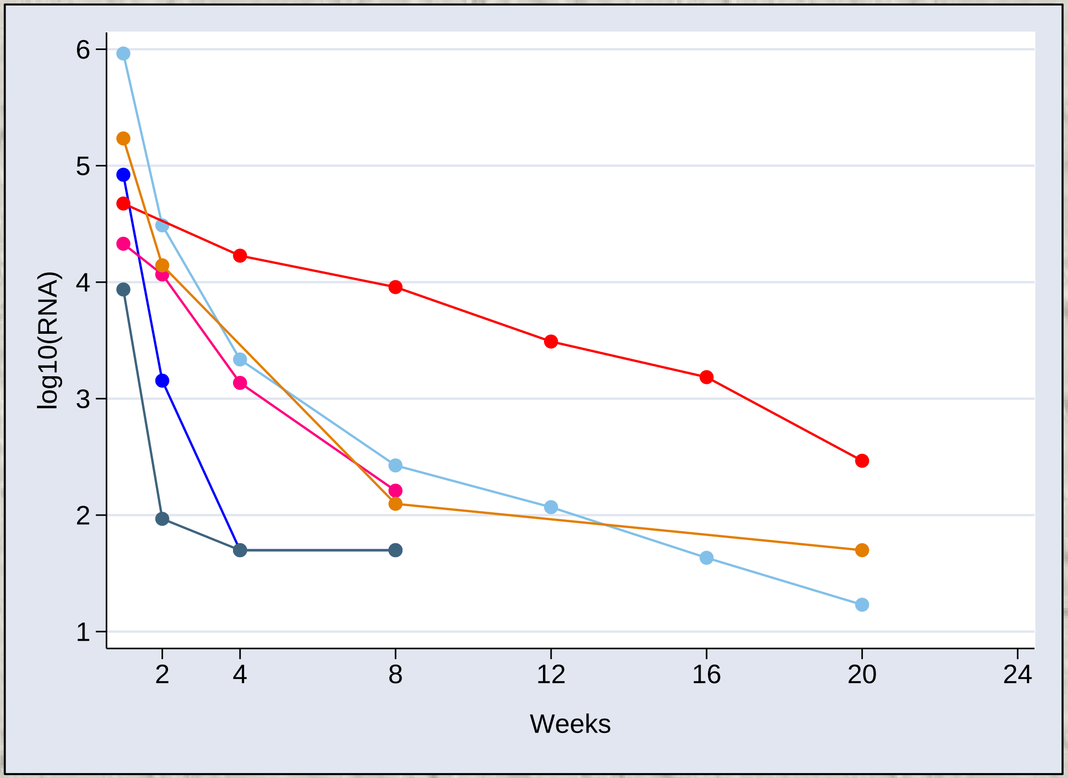
Sensitive **Resistant**

Motivation

- Wei and Johnson (1985, Biometrika)
  - Same follow-up schedule, all patients
  - Test at each time point
  - Combine across time points
- Yao, Wei and Hogan (1998, Biometrika)
  - Shift model
  - Incomplete repeated measures
  - Informative censoring
  - Does not require same follow-up schedule
- Others ...

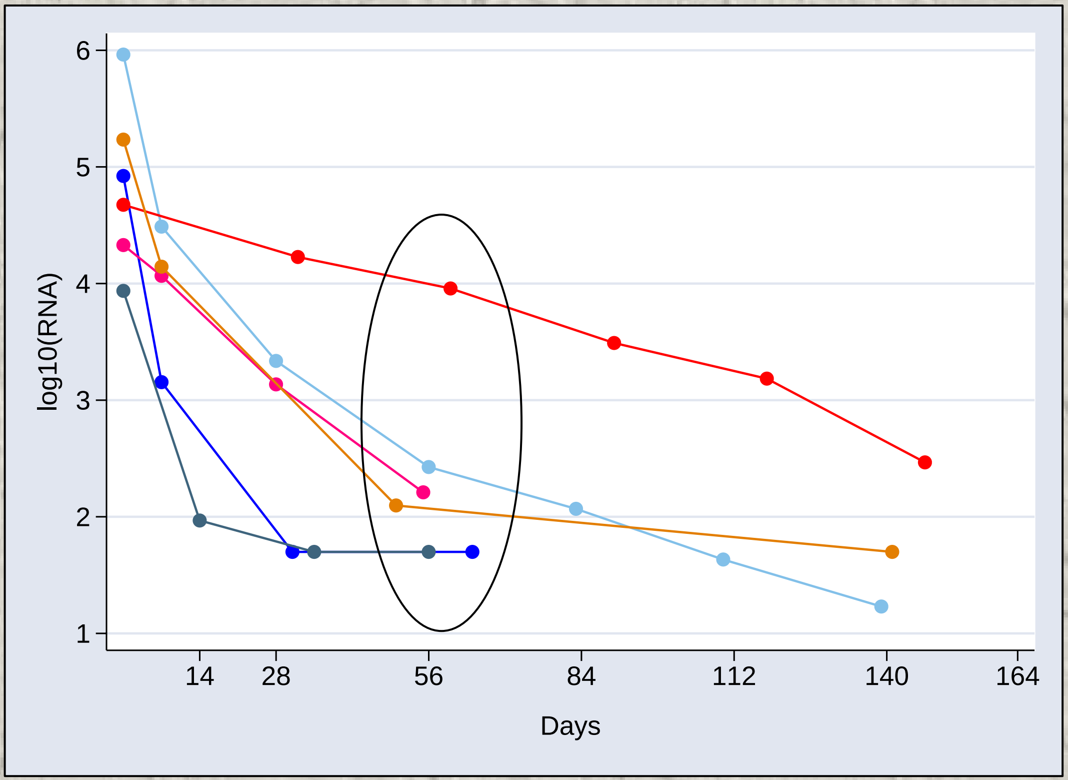
Motivation

- **Same follow-up schedule**



Motivation

- ... in reality



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New Tests

- **Assume for sensitive and resistant groups**

$$X_{ik} = \mu(t_{ik}) + \varepsilon_i(t_{ik}) \qquad i = 1,\ldots,m \quad k = 1,\ldots,c_i$$

$$Y_{j\ell} = \eta(t_{j\ell}) + \delta_j(t_{j\ell}) \qquad j = 1,\ldots,n \quad \ell = 1,\ldots,c_j$$

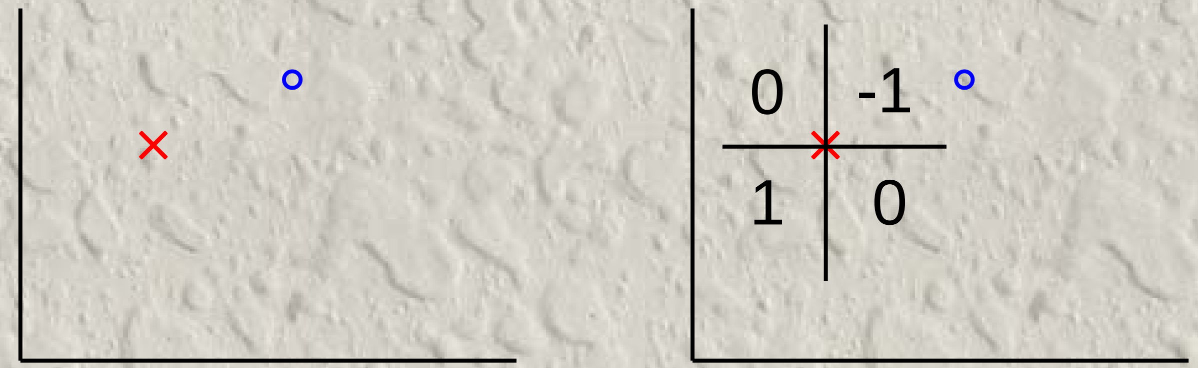
- **Hypothesis**

  H_0: $\mu(t) = \eta(t)$

  H_A: $\mu(t) = \eta(t) + \rho(t)$ **,** $\rho(t) > 0$ **or** $\rho(t) < 0$

New Tests

- **General idea**



- **Score**

$$= \begin{cases} 1 & \text{if } X_{ik} < Y_{j\ell} \text{ and } t_{ik} \le t_{j\ell} \\ -1 & \text{if } X_{ik} > Y_{j\ell} \text{ and } t_{ik} \ge t_{j\ell} \\ 0 & \text{otherwise} \end{cases}$$

Test 1

- **Test statistic**

$$U_1 = \frac{1}{mn}\sum_{i=1}^{m}\sum_{k=1}^{c_i}\sum_{j=1}^{n}\sum_{\ell=1}^{c_j}\Theta\Big(\big(X_{ik},t_{ik}\big),\big(Y_{j\ell},t_{j\ell}\big)\Big)-\hat{\theta}_{ikj\ell}$$

where $\hat{\theta}_{ikj\ell}$ **estimates** $E\Big[\Theta\Big(\big(X_{ik},t_{ik}\big),\big(Y_{j\ell},t_{j\ell}\big)\Big)\Big]$

$$\Theta\Big(\big(X_{ik},t_{ik}\big),\big(Y_{j\ell},t_{j\ell}\big)\Big)=\begin{cases}1 & \text{if } X_{ik}<Y_{j\ell} \text{ and } t_{ik}\le t_{j\ell}\\ -1 & \text{if } X_{ik}>Y_{j\ell} \text{ and } t_{ik}\ge t_{j\ell}\\ 0 & \text{otherwise}\end{cases}$$

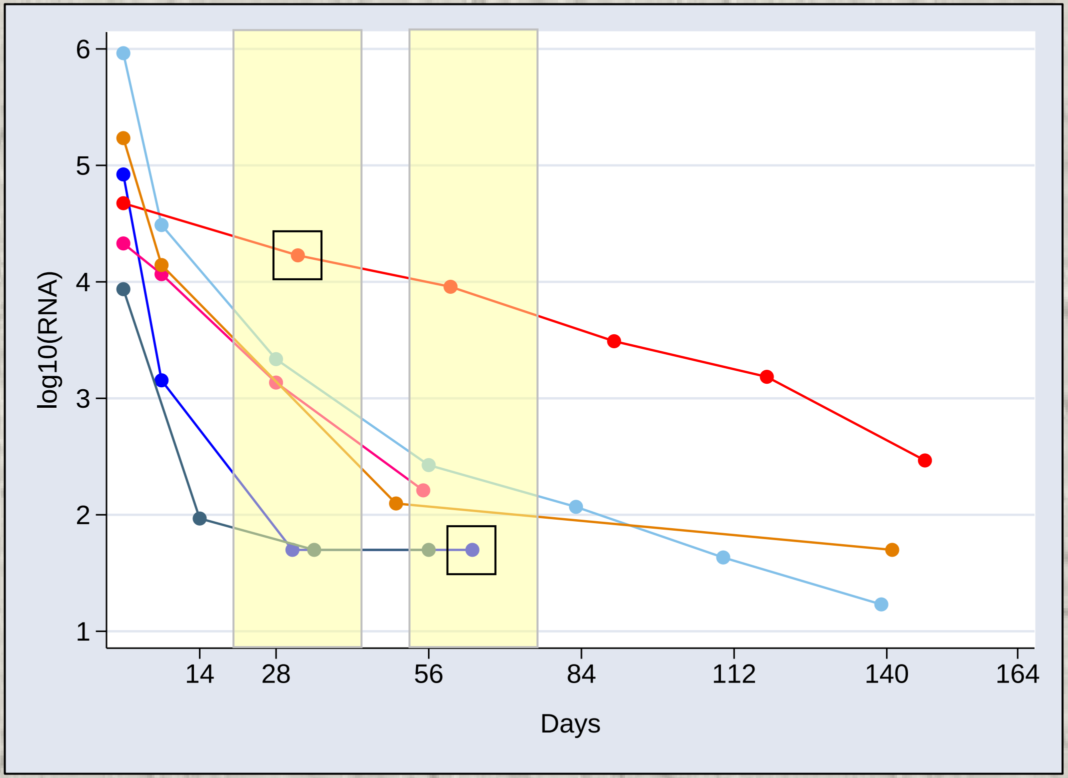
Test 1

- **How to estimate** $E\left[\Theta\left(\left(X_{ik},t_{ik}\right),\left(Y_{j\ell},t_{j\ell}\right)\right)\right]$ **?**
  - **Form intervals** I_{ik} **and** $I_{j\ell}$ **around** t_{ik} **and** $t_{j\ell}$
  - **Calculate scores**
  - **Use all observations in intervals**
  - **Divide by number of scores**
  - **Separately for each group, then combine**

$$\hat{\theta}_{ikj\ell} = \sum_{t_{i^*k^*}\in I_{ik}} \sum_{t_{j^*\ell^*}\in I_{j\ell}} \Theta\left(\left(Z_{i^*k^*},t_{i^*k^*}\right),\left(Z_{j^*\ell^*},t_{j^*\ell^*}\right)\right) \Big/ d_{I_{ikj\ell}}$$

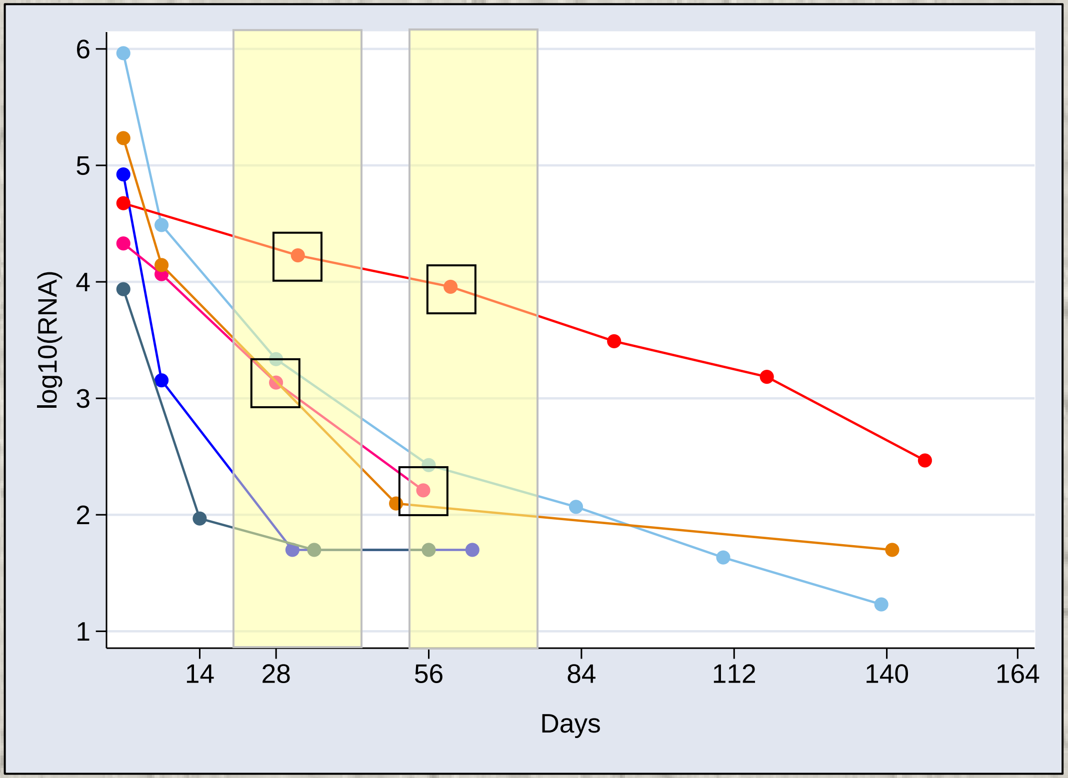
Test 1

- **How to calculate the expected score**



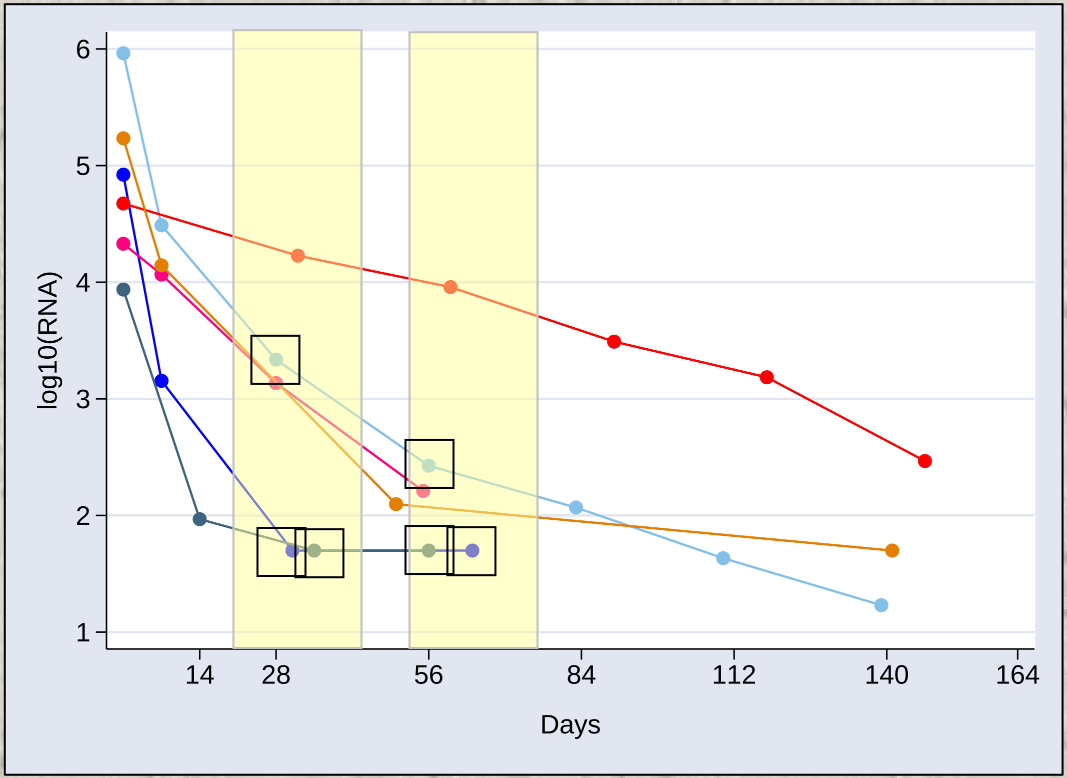
Test 1

- **How to calculate the expected score**



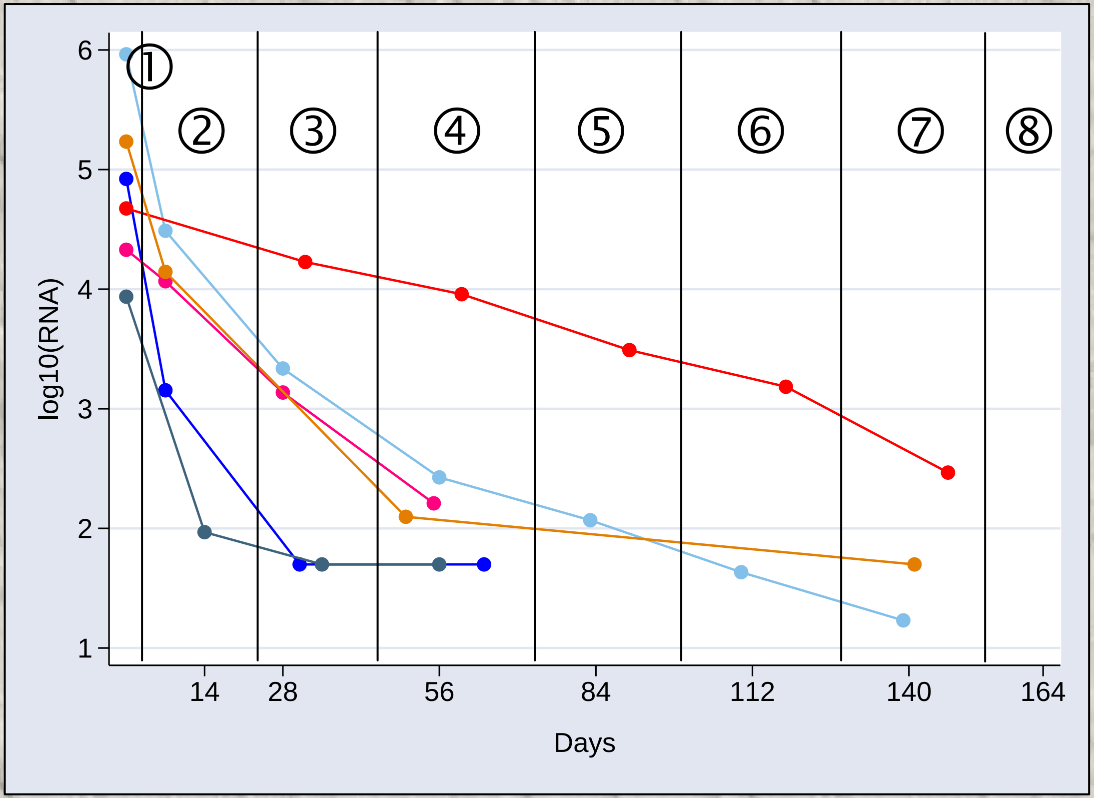
Test 1

- **How to calculate expected score**



Test 2

- **Form "bins" around follow-up visits**



Test 2

- **Score within bins**
- **Weight by inverse of covariance matrix**
- **Assume discrete number of time points**

$$U_3 = \frac{\sqrt{m+n}}{mn} \sum_{i=1}^{m} \sum_{j=1}^{n} \left(\Theta_{i1j1} - \hat{\theta}_{i1j1}, \ldots, \Theta_{iBjB} - \hat{\theta}_{iBjB} \right) \Sigma^{-1} \begin{pmatrix} \Theta_{i1j1} - \hat{\theta}_{i1j1} \\ \vdots \\ \Theta_{iBjB} - \hat{\theta}_{iBjB} \end{pmatrix}$$

$$\sigma_{pq}^2 = \frac{m+n}{(mn)^2} \sum_{m_p \times n_p} \sum_{m_q \times n_q} \left(\Theta\left(X_{ip}, Y_{jp}\right) - \hat{\theta}_{ipjp} \right) \left(\Theta\left(X_{i'q}, Y_{j'q}\right) - \hat{\theta}_{i'qj'q} \right)$$

- **Obtain *p*-values via re-sampling**

Censored observations

- **Due to measurement limits**

$$\textbf{Score} = \begin{cases} 1 & \text{if } X_{ik} < Y_{j\ell} \text{ and } t_{ik} \le t_{j\ell} \\ & \textbf{and } \boldsymbol{X} \textbf{ is not censored from above} \\ & \textbf{and } \boldsymbol{Y} \textbf{ is not censored from below} \\ -1 & \text{if } X_{ik} > Y_{j\ell} \text{ and } t_{ik} \ge t_{j\ell} \\ & \textbf{and } \boldsymbol{X} \textbf{ is not censored from below} \\ & \textbf{and } \boldsymbol{Y} \textbf{ is not censored from above} \\ 0 & \text{otherwise} \end{cases}$$

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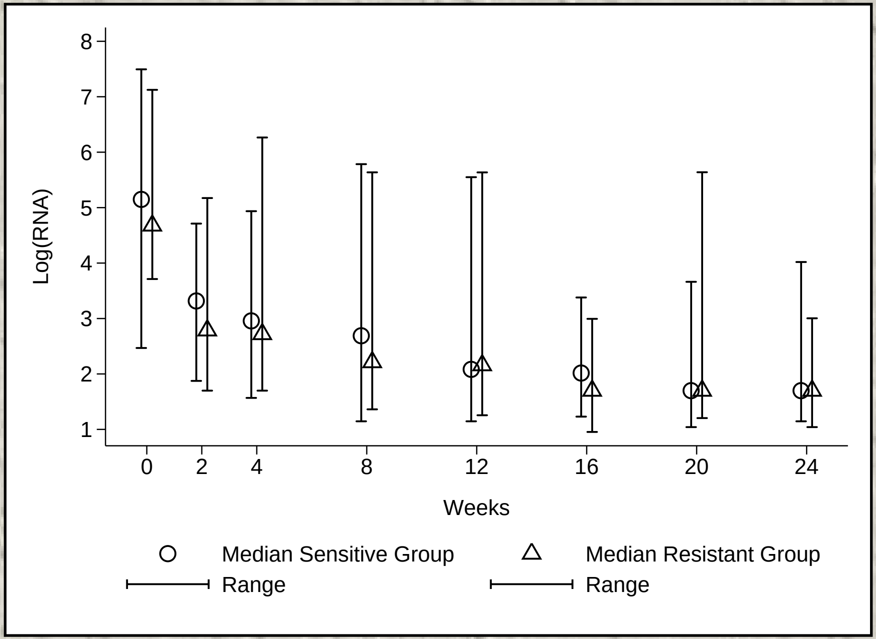
Example data – AIEDRP

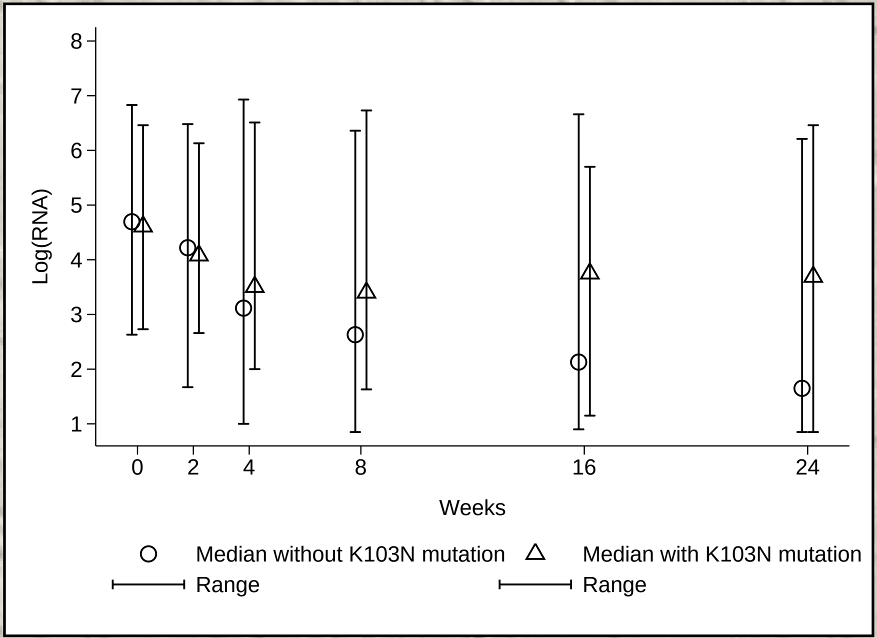
- **93 sensitive, 33 resistant patients**



- **U_1: p-value 0.22; U_3: p-value 0.20**
- **Wei-Johnson: p-value 0.30**

Example data – ACTG398

- **292 without, 64 with K103 mutation**



- ***U_3*: *p*-value 0.004**
- **Wei-Johnson: *p*-value 0.03**

Simulations

- Power: U_3 versus U_1
  - Highly correlated responses over time
  - U_3 higher power than U_1
- Power: U_3
  - Week 2, 4, 6, linear decline
  - Re-sampling: 1000
  - Simulations: 2000
  - Differences in slope -15.0, -10.0, -7.5, -5.0
  - SD: 11.8
  - Autoregressive(1) covariance, $\rho = 0.7$

Simulations – cont.

- **Power: various effect sizes**

Diff in β	Total sample size		
	N = 20	*N* = 60	*N* = 80
-15.0	0.44	0.68	0.86
-10.0	0.32	0.53	0.70
- 7.5	0.27	0.42	0.58
- 5.0	0.19	0.29	0.46

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Asymptotics

- *"aU"*-statistics (*a*lmost *U*-statistics)
- Kernel includes unknown parameter
- Randles (1982) or Lee (1990)
- U_3 is asymptotically $\chi^2_{(B)}$

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Comparison to other tests

- Yao, Wei and Hogan (1998, Biometrika)
  - Shift model
  - Allow for informative censoring (horizontal)
  - Do not make use of covariance to improve on efficiency
  - Variance estimates depend on estimated shift parameter

Comparison to other tests

- Functional ANOVA
  - Does not rely on parametric assumptions
  - Modeling longitudinal data using splines

  - Is not invariant to monotone transformations of outcome or time
  - Does not easily accommodate censoring of outcome values

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Summary

- Computationally intensive
- Conceptually easy
- Distributions of time points of obs do not have to be the same
- Non-parametric
- Invariant to monotone transformations of data

Summary – cont.

- Prob of missing obs can depend on outcome value if same in both groups
- Censoring (e.g. of RNA values) can be accommodated easily

- Variation: score within bins and across neighboring bins
- Inverting
- Regression

May S. and DeGruttola V. (2007) “Nonparametric Tests for Two Group Comparisons of Dependent Observations Obtained at Varying Time Points”, *Biometrics,* 63, 194 - 200*.*

Funded by: U01 AI043638 and R01 AI 51164

Thanks to

- Lin Liu
- Ron Thomas
- LJ Wei
- Ed Gehan

Thank you!