Repeated Measures Analysis of the Relationship between Genotypic Sensitivity and MEMS Adherence with Viral Suppression

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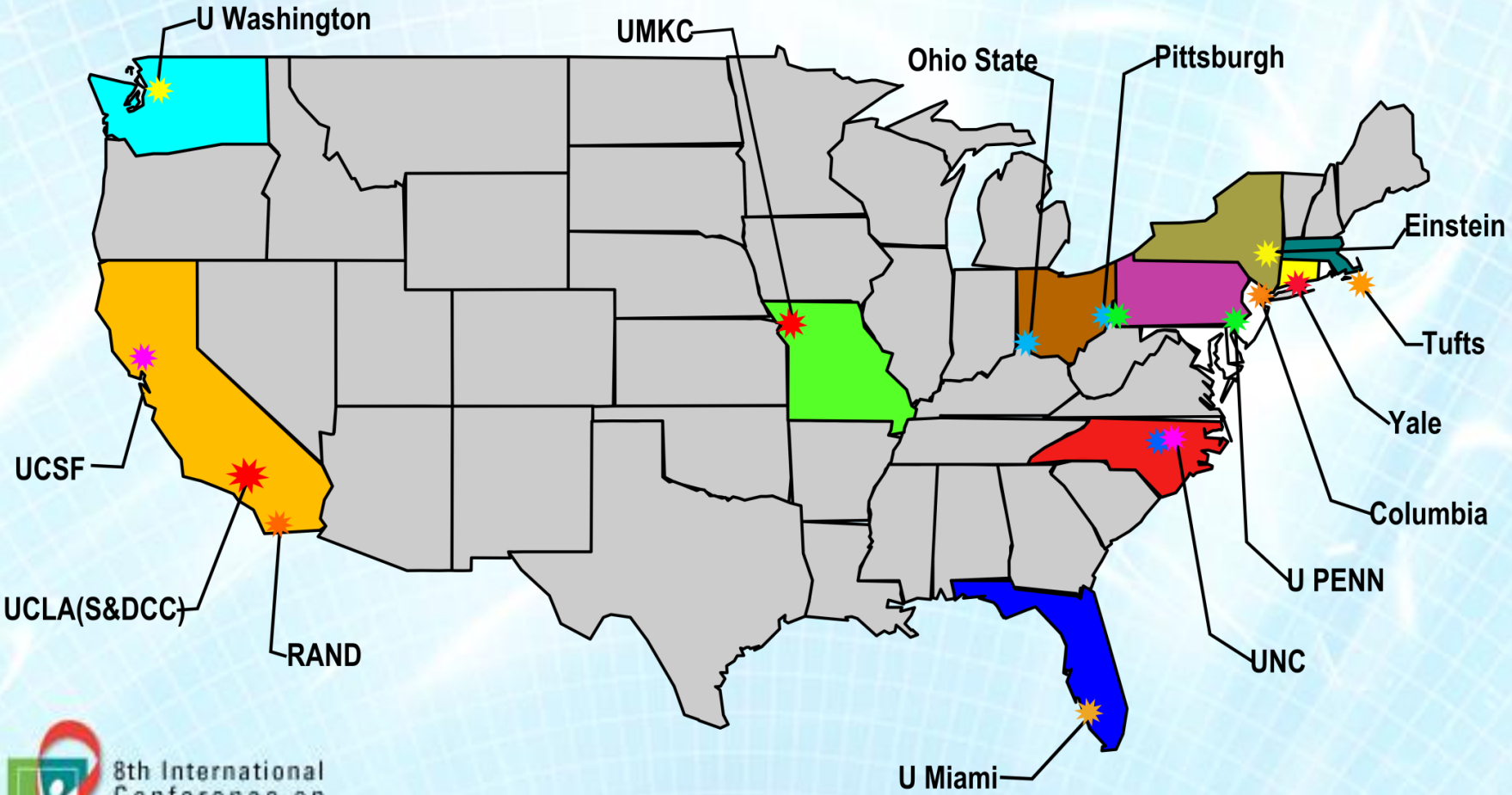
14 Sites of MACH14



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5 Studies Collected Resistance Data

Institute	Study Name	Project	No. of Subjects	Length
University of Missouri-Kansas City	ART Adherence: Enhanced Counseling and Observed Therapy	2004-2008	202	12 months
University of North Carolina at Chapel	Directly Observed Therapy (DOT)	2000-2005	102	12 months
Yale University	Rewards Improve Medication Compliance for HIV Treatment (REWARDS)	2002-2005	97	9 months
University of California, Los Angeles	Adherence and Efficacy of Protease Inhibitor Therapy (ADEPT)	1997-2000	145	12 months
University of California, San Francisco	Research in Access to Care in the Homeless (REACH)	1997-2002	108	60 months

Inclusion Criteria

- Include all the patients with MEMS adherence measurements, drug resistance information, and viral load counts over time

- A total of 380 patients included in the analysis

Rationale

- Adherence to the HAART regimen is a major determinant of drug concentration and a key predictor of lack of virologic suppression.
- HIV drug resistance is crucial in HIV viral load suppression and in control for secondary infection
- Few studies have assessed the relation between adherence, emergence of resistance and viral load with a large sample size

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Adherence to ARV

- Calculated based on 4–week intervals:
  - $Adh = \frac{\text{\# of observed openings}}{\text{\# of expected openings}}$
- At patient level as the average across different ARVs.
- Truncated at 100%.

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Drug Resistance

- The MACH14 resistance data contained 1906 mutation observations, collected from 1997-2008 across the 5 studies.
- AntiRetroScan version 2.x (2009) (developed at the University of Siena HIV) Monitoring Service was used to calculate resistance scores.
- The accuracy of AntiRetroScan >=the commonly used genotypic antiretroviral resistance interpretation systems (Stanford HIVdb, ANRS, Rega).

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http://www.hivarca.net/includeGenPub/AntiRetroScan_2x.htm

Zazzi M, et.al. Rules-based HIV-1 genotypic resistance interpretation systems predict 8-week and 24-week virological antiretroviral treatment outcome and benefit from drug potency weighting. J Antimicrob Chemother 2009;64:616-24.

Drug Resistance Score

- We use 4 levels of GSS for combined regimen from a given patient. The higher GSS, the more sensitive to the combined regimen.

GSS	Frequency	Percent	Cumulative Frequency	Cumulative Percent
0	11	0.58	11	0.58
1	44	2.31	55	2.89
2	91	4.77	146	7.66
3	1760	92.34	1906	100.00

Viral Load

- A total of 1851 viral load data points across patients and across time available (measured in copies/mL approximately every 4 weeks)
- Undetectable viral load was defined as <50 copies/mL.
- log(VL) was used in analyses.

Variable	N	Mean(std) or %	Range
Age	379	40.53(8.09)	21-69
Gender			
Male	219	58.56	
Female	155	41.44	
Ethnicity			
White	75	19.74	
African American	181	47.63	
Hispanic	65	17.11	
Other	59	15.53	
Education			
<HS	117	30.87	
HS	231	60.95	
>HS	31	8.18	
Income			
<10K	243	65.32	
10K-30K	92	24.73	
>30K	29	7.79	
Regimen			
PI	129	33.95	
Boost	39	10.26	
NNRTI	88	23.16	
Other	124	32.63	
Naïve			
Naïve	269	71.35	
Not naïve	108	28.65	
Substance			
Use	185	72.83	
Not use	69	27.17	

Characteristics of 380 subjects

Correlations between GSS, Adherence and VL

- A total of 1906 observations from 380 subjects, with viral load readings, resistance data, MEMS adherence available.

  - r(GSS, % adherence)=0.15 ($p<0.001$)
  - r(GSS, VL)= – 0.24 ($p < 0.0001$)
  - r(% adherence, VL)= – 0. 16 ($p< 0.0001$)

Model

- Repeated measures mixed effects method was used to model the relationship between the Viral load, MEMS adherence, and Genotypic Sensitivity Score

- Other Covariates: Time , CD4 counts, Naïve to ARV at baseline, Use substances, and Demographics (age, gender, ethnicity, education)

Effect		Estimate	Standard Error	Pr > |t|
Intercept		15.8918	1.6498	<.0001
Adherence (0-1)		-5.7497	2.0570	0.0060
GSS		-2.0792	0.5120	<.0001
adh*GSS		1.5531	0.7088	0.0302
Study time		-0.00085	0.000959	0.3773
cd4_result		-0.00089	0.000418	0.0346
age		-0.02986	0.01542	0.0550
Gender	Ref: Male	-0.2578	0.2548	0.3134
Naïve	Ref: Naïve	-0.08587	0.3186	0.7879
race	AA	-0.5555	0.3827	0.1490
(Ref: White)	Latino	-0.5638	0.4779	0.2403
	Other	-1.1990	0.4371	0.0069
Education	< HS	0.1531	0.2412	0.5267
(Ref: High school)	> HS	0.2091	0.5128	0.6841
Substance	Ref: use	0.1889	0.3235	0.5602

Model

- Repeated measures mixed effects model:
  - Log (VL) = 15.89 – 5.75*adh – 2.08*GSS + 1.55*adh*GSS + Other Covariates

- 10% increase in adherence --> 0.57 decrease in log viral load when a patient has drug resistance to all his/her drugs (GSS=0), holding all other variables as constant.

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Interpretation of Model

- Compare at different GSS levels with perfect Adherence
  - GSS=0, Log(VL) = intercept – 5.75*Adh = intercept – 5.75
  - GSS=1, Log(VL) = intercept – 4.20*Adh – 2.08 = intercept – 6.28
  - GSS=2, Log(VL) = intercept – 2.64*Adh – 4.16 = intercept – 6.81
  - GSS=3, Log(VL) = intercept – 1.09*Adh – 6.24 = intercept – 7.34

- Conclusion: adherence will be less effective on VL suppression when the GSS level is lower.

Interpretation of Model

- Compare at different Adherence level
  - 100% adherence, Log(VL) = intercept – 5.75 – 0.53*GSS
  - 90% adherence, Log(VL) = intercept – 5.72– 0.69*GSS
  - 80% adherence, Log(VL) = intercept – 4.60 – 0.84*GSS

- Conclusion: the effect of drug resistance on VL suppression is non-linear

Take Home Message

- Adherence will be less effective for VL controlling when drug resistance is high.
- With varying levels of adherence, drug resistance has a non-linear impact on VL suppression.
- Keeping good adherence is important even if drug resistance has already been developed for one or more ARVs.

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Future Direction

- Compare AntiRetroScan with other newer version of software available for GSS calculation
- Need to carefully evaluate the impact of missing data on our model fitting

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