NORTHWEST AIDS EDUCATION AND TRAINING CENTER

Update from CROI, 2012, Seattle

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Update from CROI, 2012, Seattle

- Conference included 1157 oral abstracts, posters and late-breakers
- For a full listing of abstracts including web and pod-casts go to: http://retroconference.org/

Update from CROI, 2012, Seattle

Today:

- Latent Reservoir, Neuro-HIV and Metabolic Issues

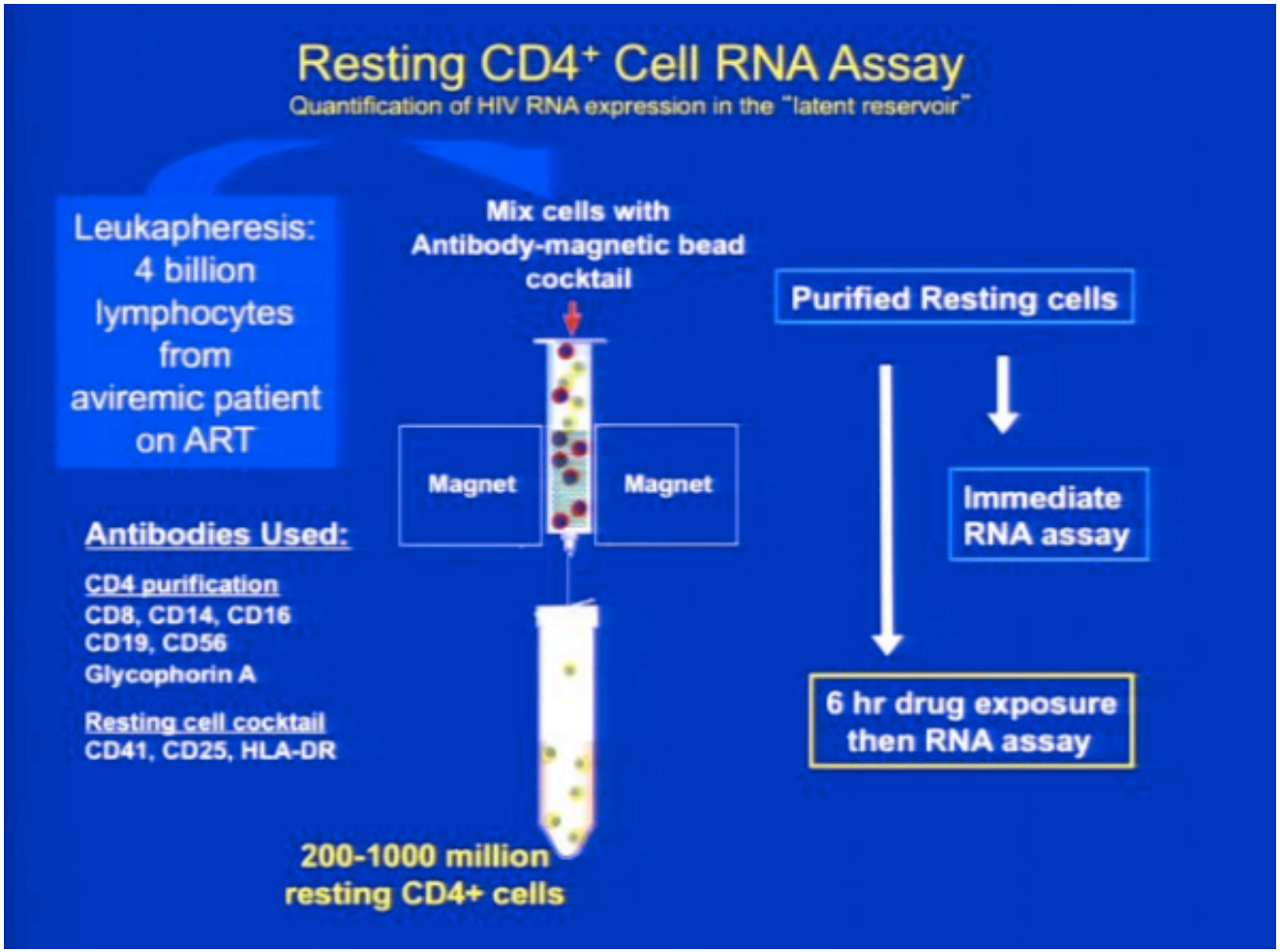
Future sessions:

- ARV treatment and HCV: David Spach
- Prevention: Jared Baeten

Administration of Vorinostat Disrupts HIV-1 Latency in Patients on ART

- Resting CD4+ T cells primary reservoir of persistent infection
- Histone deacetylases maintain latency
- HDAC inhibitor suberoylanilide hydroxamic acid (SAHA) (aka Vorinostat) induces expression of latent HIV from resting CD4+ T cells ex vivo

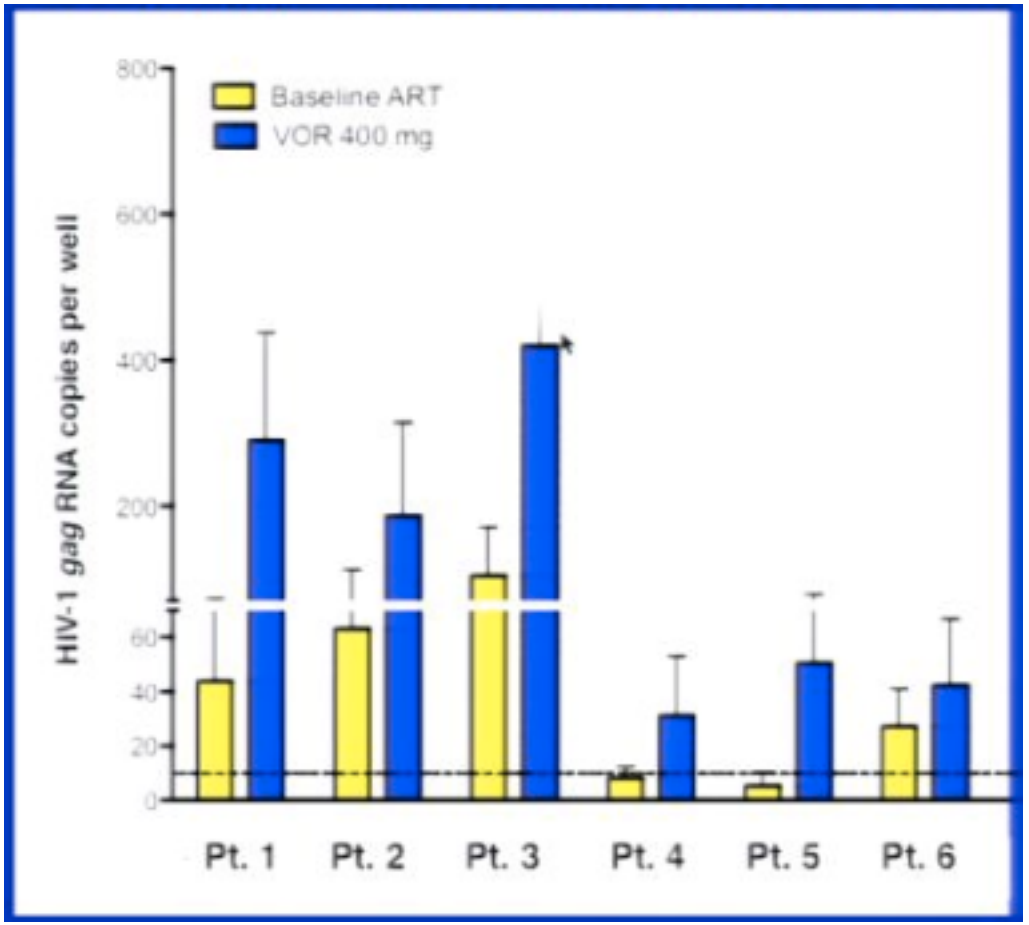
Vorinostat and HIV-1 Latency: Single Dose Proof of Concept Study



David Margolis et al

Vorinostat Disrupts HIV-1 Latency in Patients on ART

- RESULTS:
- Mean 4.8-fold induction
- No AE's
- No change in single copy RNA expression

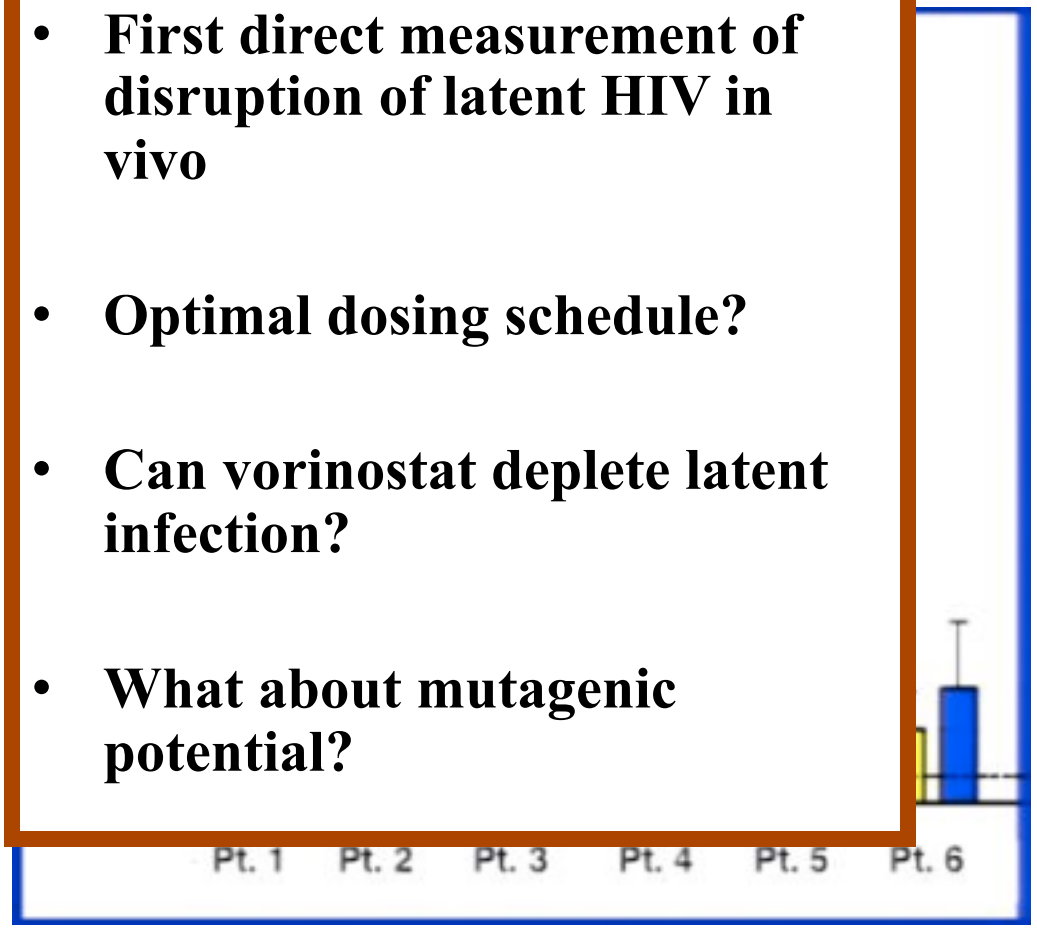


Vorinostat Disrupts HIV-1 Latency in Patients on ART

RESULTS:

- Mean 4.8-fold induction
- No AE's
- No change in single copy RNA expression

- **First direct measurement of disruption of latent HIV in vivo**
- **Optimal dosing schedule?**
- **Can vorinostat deplete latent infection?**
- **What about mutagenic potential?**



Asymptomatic Mild HAND Increases the Risk for Future Symptomatic Decline: A CHARTER Study #77

- HIV Associated Neurocognitive Disorder (HAND) is present in 30-50% of patients

- Question: Does ANI confer a risk of progression to MND or HAD?
- N=347; 226 neuropsychologically normal, 121 ANI. Completed rigorous neurocognitive assessments every 6 months

Asymptomatic Mild HAND Increases the Risk for Future Symptomatic Decline: A CHARTER Study #77

- Self Reporting (SR)Tests
  - Partial Assessment of Own Functioning Inventory (PAOFI)
    - Measures 5 cognitive domains: Symptomatic: > 3 complaints
  - Activities of Daily Living (ADL)
    - Measures independence in completing basic activities of daily living: Symptomatic: decline in > 2 areas
  - Need both tests to be abnormal to be classified as symptomatic
- Performance Based (PB) Tests
  - Medication Management Test-Revised (MMT-R)
    - Measures ability to perform tasks related to med management (e.g. fill a mediset). Symptomatic score: > 1 SD from the mean of normal
  - Valpar System 3000 Work Samples and Computerized Assessment
    - Measure abilities important for completing work related activities. Symptomatic score: > 1 SD from the mean of normal

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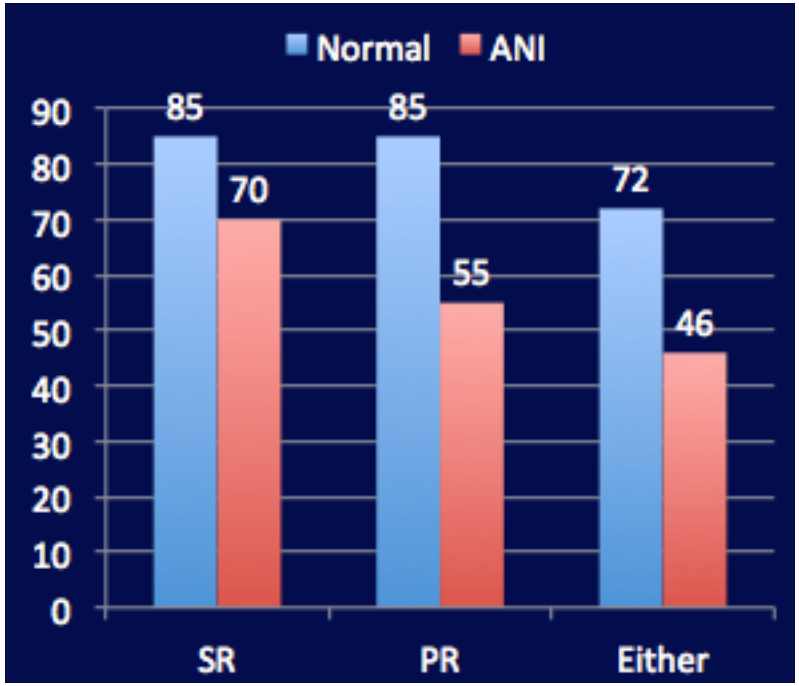
Vorinostat Disrupts HIV-1 Latency in Patients on ART

- Baseline characteristics of Normal Vs ANI:
- Well matched by age, gender, race, education, substance abuse, % AIDS, current CD4, % on ARV and % HCV infected.
- ANI patients had more co-morbid conditions (45 Vs 23%) and lower CD4 nadir (162 Vs 201)

Percent Asymptomatic at 80 – 90 months



Asymptomatic Mild HAND Increases the Risk for Future Symptomatic Decline: A CHARTER Study #77

- Baseline Predictors of Decline in Cognitive Function
- Yes: Older age, less education, female sex, substance abuse, co-morbid conditions, AIDS dx, CD4 nadir and HCV infection
- No: Ethnicity, ARV treatment, current CD4, estimated duration of HIV infection

Vorinostat Disrupts HIV-1 Latency in Patients on ART

Time Dependent Correlates of Decline in Cognitive Function

	Multivariable Analysis	
Self Report	Relative Risk	P-value
ANI Vs NML	2.81	.0001
Current MDD	3.00	.001
Performance Based		
ANI Vs NML	5.17	< .00001
Current CD4	1.21	.0006
SR or PB		
ANI Vs NML	3.41	< .00001
Current CD4	1.10	.021

ARV Rx, ARV type, CPE score, VL, CSF VL and substance abuse were all NS in univariable analysis

Asymptomatic Mild HAND Increases the Risk for Future Symptomatic Decline: A CHARTER Study #77

Conclusions

1. Patients with ANI have a 3-5 RR of developing symptomatic HAND compared to normal pts even after adjusting for baseline predictors
2. Earlier cognitive decline is more common in women, those with substance abuse and other co-morbid conditions and those with a lower CD4 nadir, an AIDS dx, HCV infection and lower follow up CD4 counts

Effect of Statins on Reducing the Risk of Serious Non-AIDS Defining Events and Non-accidental Death (ACTG/ALLERT), #124

ALLRT Cohort

(ACTG Longitudinal Linked Randomized Trials)

- This study: Determine the effect of statins on the outcome of non-AIDS End Organ Disease
- N = 3601 patients not on a statin initially
- 481 started a statin
- Did not include outcomes that occurred in the first 8 weeks on a statin

Effect of Statins on Reducing the Risk of Serious Non-AIDS Defining Events and Non-accidental Death (ACTG/ALLERT),

ALLRT Cohort: Baseline Characteristics

Baseline Characteristic	N = 3601
Median Age	39
Gender: M/F	83%/17%
Race Black, non Hispanic White, non Hispanic Hispanic	 30% 47% 21%
Median BMI	25
Current smoker	38%
Median systolic BP	120 mm Hg
Median LDL	106 mg/dL
CD4 nadir	180 cells/mL
CD4 current	346 cells/mL
Initiated a statin	481

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Effect of Statins on Reducing the Risk of Serious Non-AIDS Defining Events and Non-accidental Death (ACTG/ALLERT) ALLRT Cohort: Non-AIDS Outcomes

Event	Nmb of Events	Event rate: Statin users (per 100 py)	Event rate: non-Statin users (per 100 py)	Crude HR	Baseline adjusted HR	Adjusted & weighted HR
CV event	62	0.5	0.4	1.44	0.82	0.89
Non-CV event	580	4.2	3.8	1.18	0.82	0.85
Bacterial infection	144	0.7	0.9	0.96	0.96	1.25
Incident DM	158	1.3	1.0	1.52	1.02	0.87
Renal events	135	1.4	0.7	1.58	1.00	0.85
Cancer	89	0.5	0.5	1.03	0.71	0.43
Death	143	0.5	0.9	0.47	0.41	0.82

Effect of Statins on Reducing the Risk of Serious Non-AIDS Defining Events and Non-accidental Death (ACTG/ALLERT), #124

Conclusions

- Statins were associated with a non-significant (but maybe clinically meaningful) reduction in non-AIDS events and deaths
  - Consistent with a Hopkins study of 1538 patients: 3 fold reduction in death rate with statin use (More, Plos One 2011)
- Statins were associated with a significant reduction in malignancies
  - Consistent with a Kaiser study of 1554 patients: 45% reduction in NHL cases with statin use (Chao, AIDS 2011)
- The benefits of statin use increased with increasing age and higher nadir CD4 count

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Impact of Switching from AZT/3TC to TDF/FTC on BMD and Bone Metabolism in Virologically Suppressed Patients (PREPARE sub-study) # 125LB

Background

- ART initiation is associated with a 2-6% decline in BMD and greater reductions are seen in TDF containing regimens
- BMD reductions correlate with increases in biomarkers of bone turnover such as
  - CTX-1 (resorption) and osteocalcin & P1NP (formation)

- Study Aim: To track the effect of switching from AZT/3TC to TDF/FTC on BMD and on biomarkers of bone turnover

Impact of Switching from AZT/3TC to TDF/FTC on BMD and Bone Metabolism in Virologically Suppressed Patients (PREPARE sub-study) # 125LB

- A multi-center, randomized, controlled study
- N = 54 patients, all on AZT/3TC for > 2 years with suppressed viral load
- Median age 45-47, mostly white males, median CD4 ~ 490

Impact of Switching from AZT/3TC to TDF/FTC on BMD and Bone Metabolism in Virologically Suppressed Patients (PREPARE sub-study) # 125LB

Results at 48 Weeks
Percent Change in BMD

	Continue AZT/3TC		Switch to TDF/FTC		
	Median change	Within group P-value	Median change	Within group P-value	Between group P-value
Lumbar Spine	-0.18	0.91	-2.04	0.01	0.030
Femoral Neck	0.14	0.74	-1.52	0.16	0.48

Impact of Switching from AZT/3TC to TDF/FTC on BMD and Bone Metabolism in Virologically Suppressed Patients (PREPARE sub-study) # 125LB

Results at 48 Weeks

	Change in biomarker over time		P-value
	AZT/3TC	TDF/FTC	
Osteocalcin (ug/L)	0.07	7.55	< 0.0001
P1NP (ug/L)	4.36	14.07	< 0.0001
CTX (ug/L)	-0.02	0.18	0.0005

Impact of Switching from AZT/3TC to TDF/FTC on BMD and Bone Metabolism in Virologically Suppressed Patients (PREPARE sub-study) # 125LB

Conclusions

- In virologically suppressed patients on AZT/3TC; switching to TDF/FTC leads to marked increases in bone turnover
- Changes in bone turnover correlate with loss of BMD in the lumbar spine