



HIV NEUROBEHAVIORAL RESEARCH CENTER

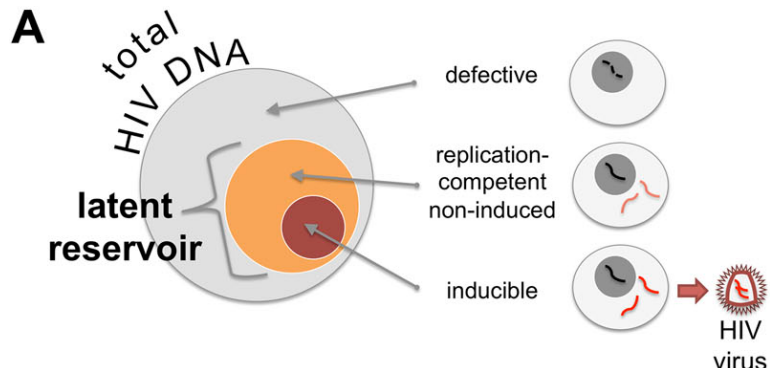
UC San Diego



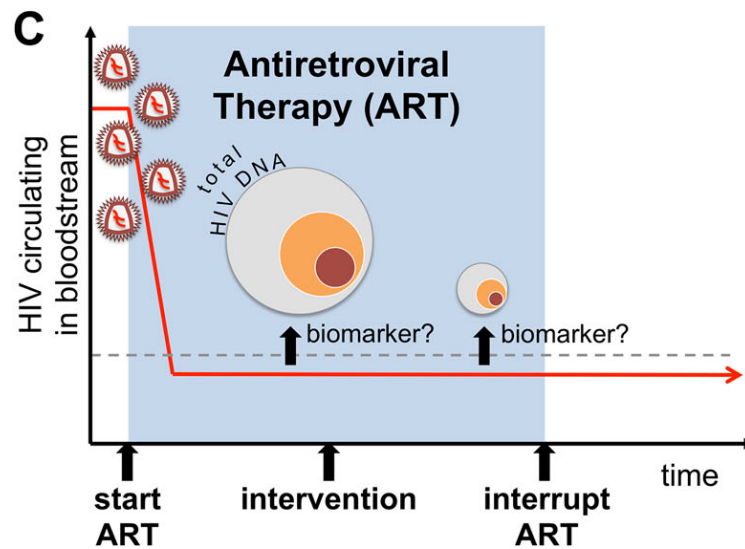
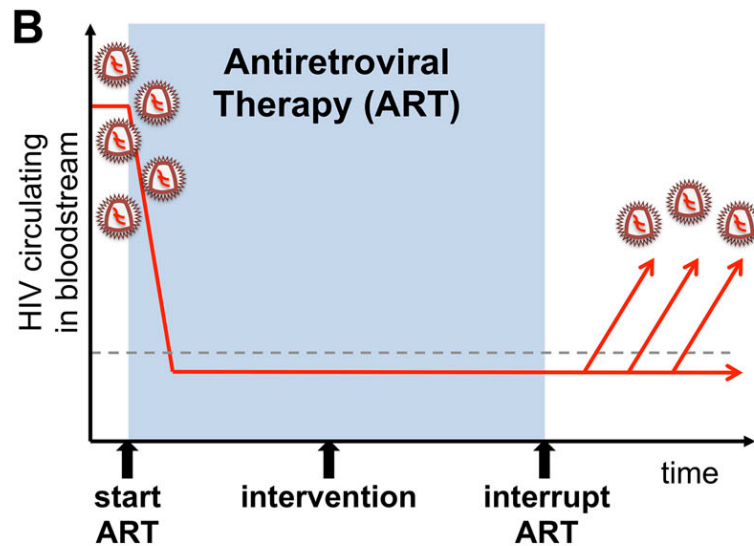
Eradication and Cure

Ronald J Ellis, MD, PhD

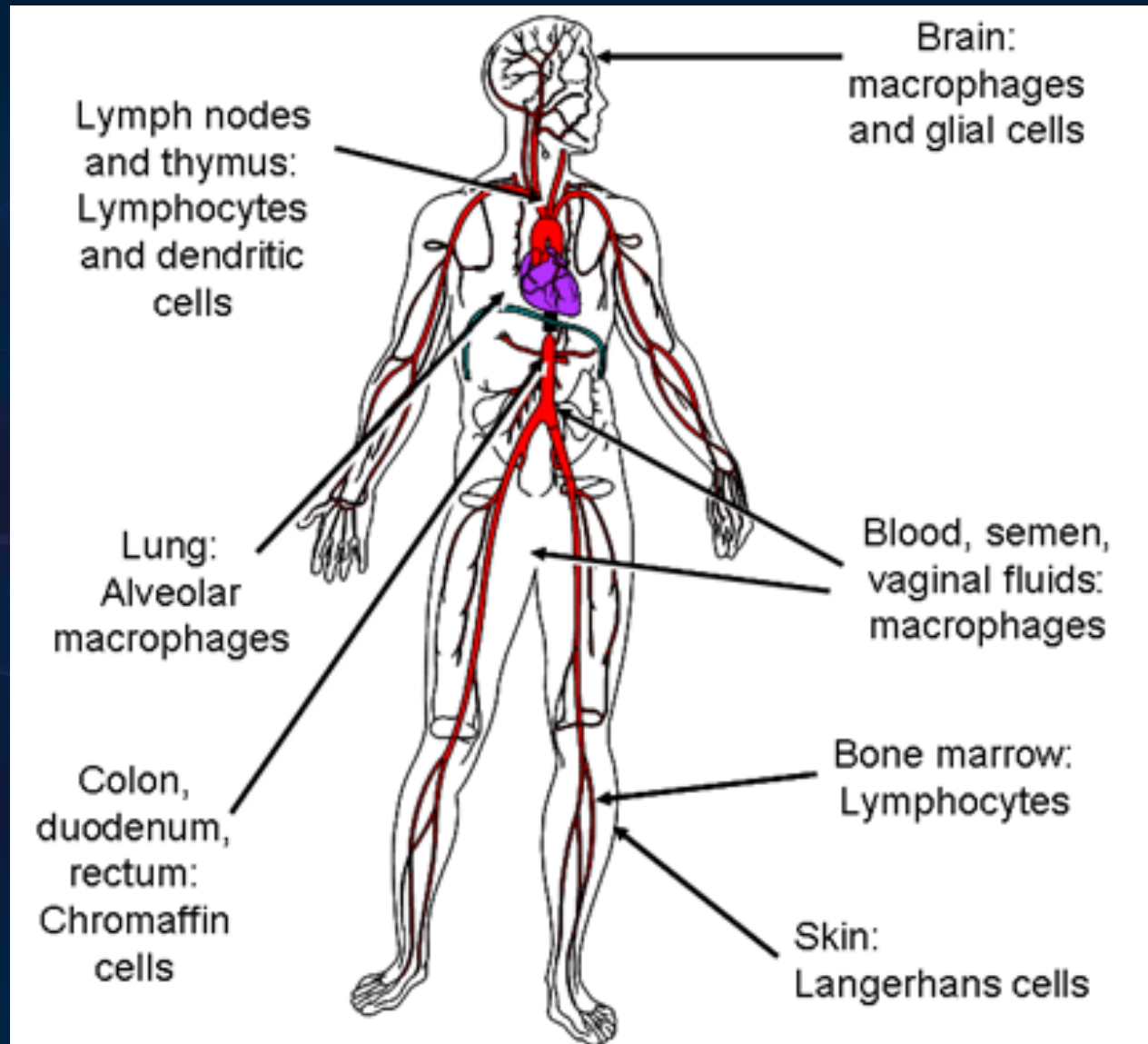
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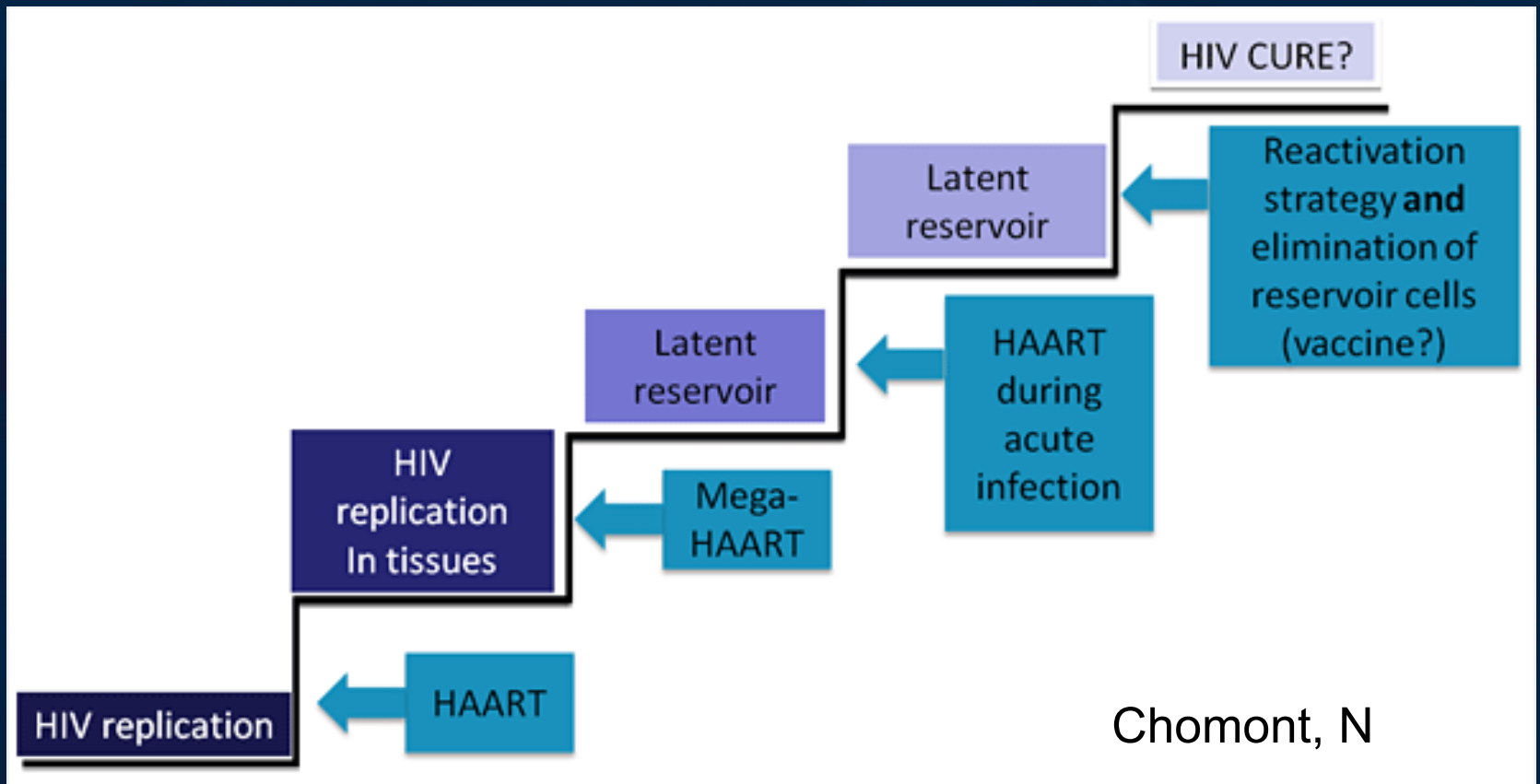
Cockerham and Deeks, 2014



HIV Reservoir Sites



Cure strategies



Unanswered questions

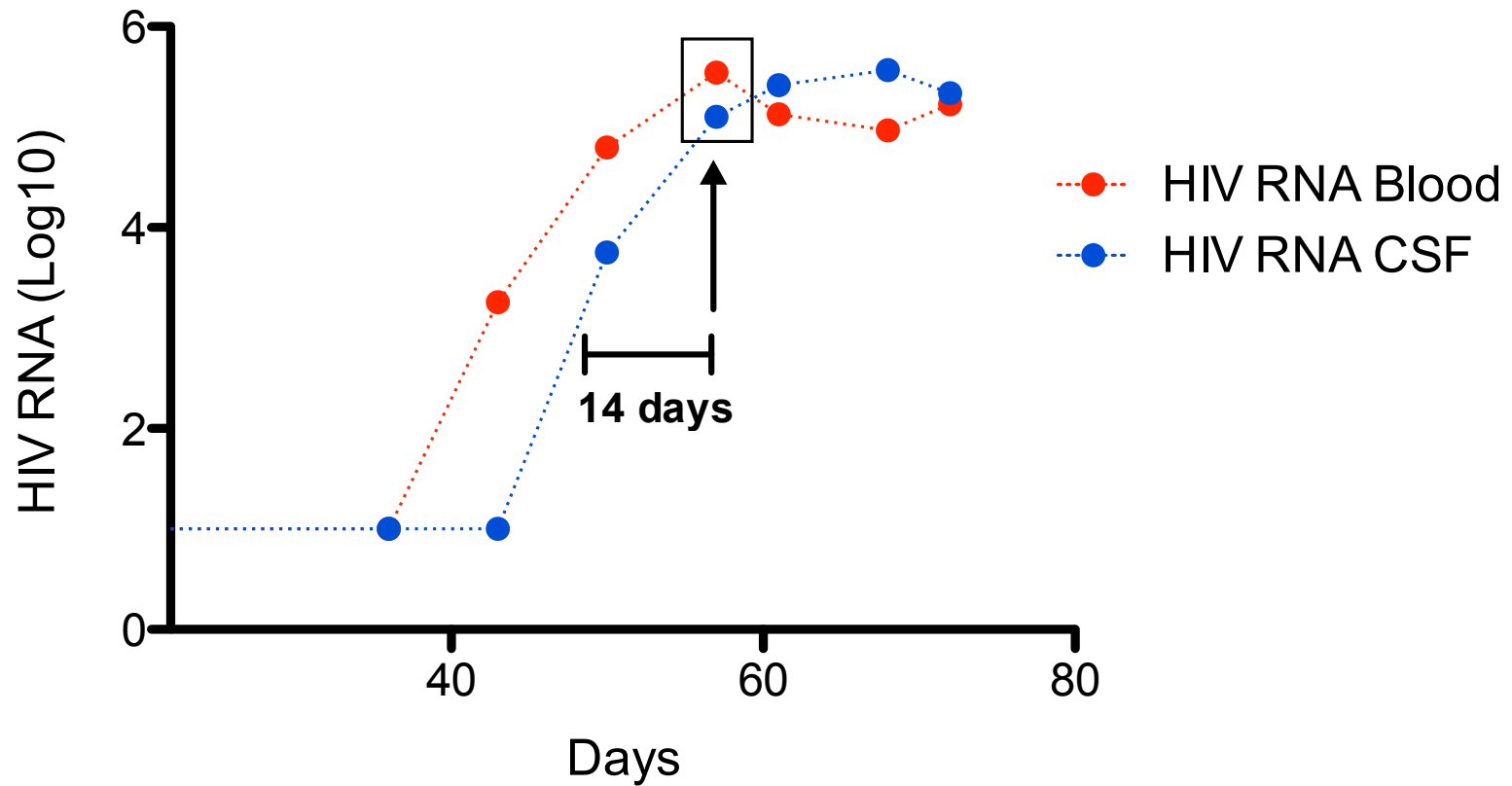
- What is the size of HIV DNA populations in the brain and where are they distributed?
 - » How much HIV DNA remains in patients with virologic suppression on ART?
- Do HIV DNA populations in the brain uniquely contribute to viral rebound following antiretroviral treatment interruption?
- Can HIV DNA in the brain be reached using “kick and kill” interventions? Will this be safe?
- Are HIV DNA populations in brain replication competent?
- Can early ART initiation and behavioral adherence interventions minimize the size of the brain HIV DNA reservoir?

What the HNRC can do to help tackle unanswered questions

- Evaluate archived CSF and blood samples from pts who underwent treatment interruption to assess whether CNS HIV DNA contributes to viral rebound
- Evaluate HIV DNA in autopsy tissue from brain bank donors who were virologically suppressed prior to death
- Characterize HIV transmission networks
- Devise and test behavioral interventions (adherence, early treatment initiation, TAP) to minimize the size of HIV DNA reservoirs at both individual and community levels

Example of Viral Rebound Dynamics

P4 viral dynamics

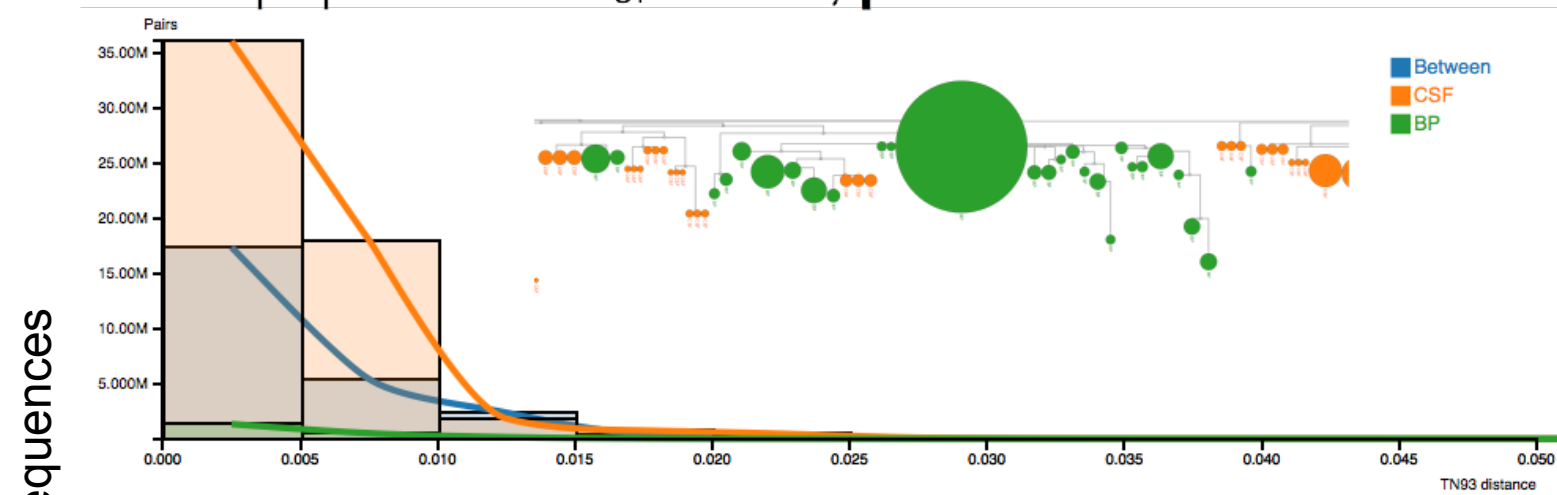


Approach

- 14 subjects interrupting ART
- Sequencing: HIV-1 env (C2-V3), gag (p24), and pol (partial RT) amplified from cell-free HIV RNA (blood and CSF).
 - Roche 454 FLX Titanium platform.
- Significance of compartmentalization: F_{ST}

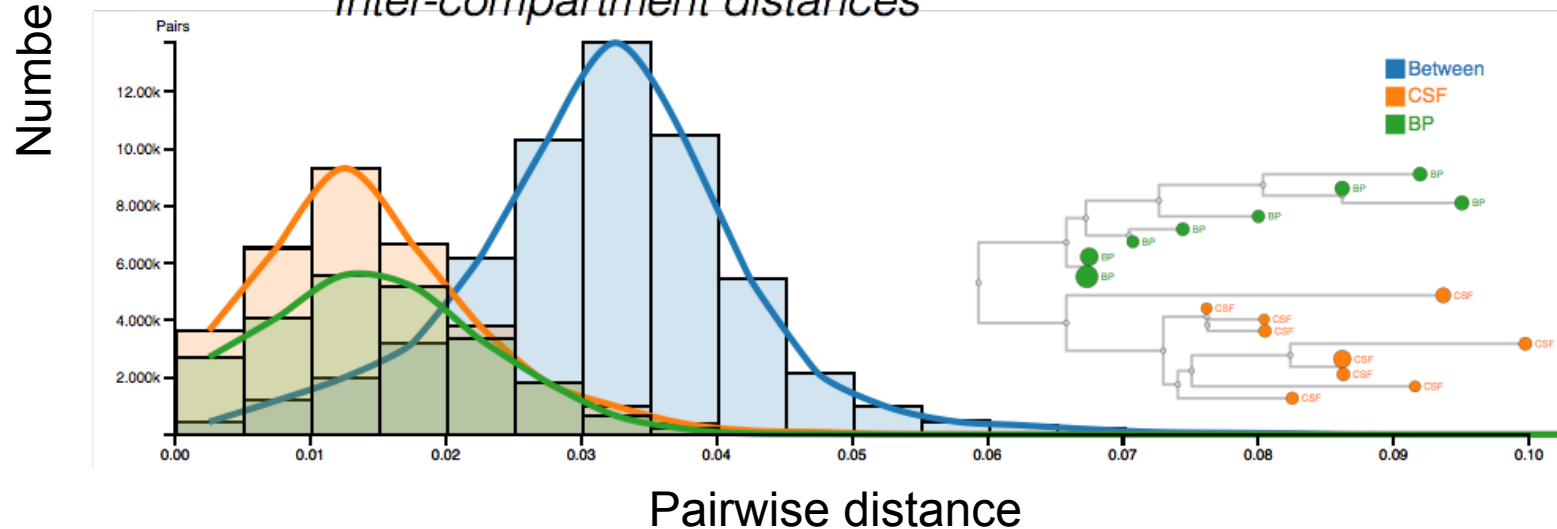
Pairwise distances and phylogenetic relationships

Mixed populations: $F_{ST} = 0.12$, $p = 0.22$



Compartmentalized populations: $F_{ST} = 0.53$, $p < 0.001$

Inter-compartment distances



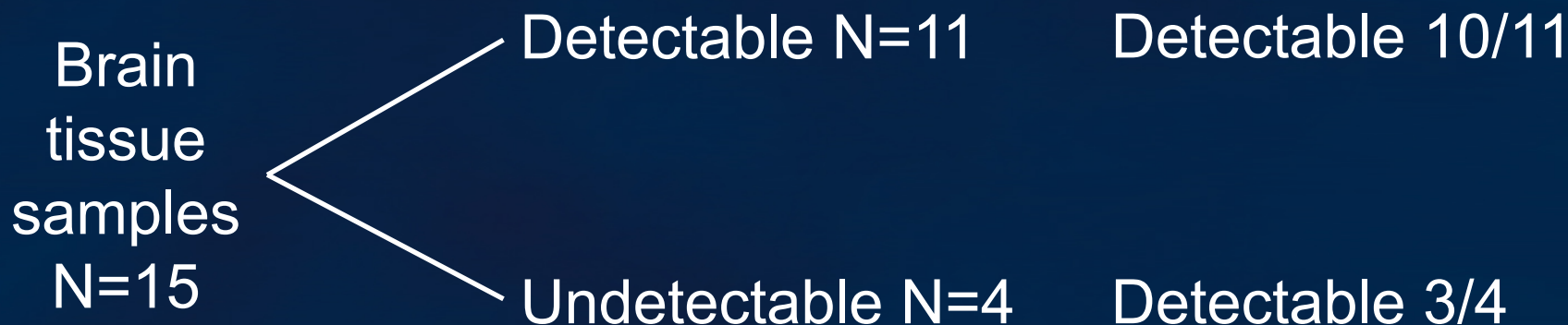
Summary

- Viral populations compartmentalized between blood and CSF In 10 / 14 pts at 1st time point assessed post-rebound
 - Of those sampled within 2 weeks, 4/4 compartmentalized
- Longitudinal change: evolution of both compartmentalization and intermixing observed.
 - Only one pt maintained genetically mixed populations for the entire study follow-up

Detecting brain HIV DNA in suppressed individuals

Antemortem
Plasma and
CSF HIV RNA

Postmortem
Brain
HIV DNA



Replication Competence in Brain Tissue

- Select cases >2y plasma HIV RNA suppression
- Extract Brain HIV DNA; amplify and dilute
- Barcode and screen for full-length (FL) sequences
- Ligate FL (N= \sim 30/sample) HIV DNA into SMRTbell (™) library complexes
- Consensus sequence FL HIV DNA
- Eliminate APOBEC hypermutation and large-scale deleted sequences
- Clone remaining intact FL HIV DNA into expression vectors
- Demonstrate infection of CD4+ T-cells and evaluate replication kinetics

Implications of this line of research

- Major point of significance is whether there is a reservoir of replication competent HIV DNA in the brain of virally suppressed individuals that needs to be specifically targeted.
- Evaluate the importance of targeting brain HIV DNA
- Behavior is central to HIV transmission and will need to be considered in devising eradication interventions

Feedback Requested

- Are there additional areas relevant to the Cure agenda to which you think the HNRC might contribute?



Thank you for your attention

Ronald J Ellis

Neuromedical Core Director
University of California, San Diego

Backup slides

Compartmentalization Results (TP1)

PID	Time (d)*	First Time-point		
		<i>gag</i>	<i>RT</i>	<i>env</i>
P1	9	No	No	Yes
P2	10	Yes	No	No
P3	11	No	Yes	Yes
P4	14	Yes	Yes	Yes
P5	16	Yes	No	Yes
P6	17	No	No	No
P7	18	Yes	Yes	Yes
P8	19	No	No	No
P9	25	No	No	Yes
P10	37	No	Yes	Yes
P11	104	No	No	No
P12	137	No	No	No
P13	150	Yes	Yes	Yes
P14	175	Yes	Yes	Yes