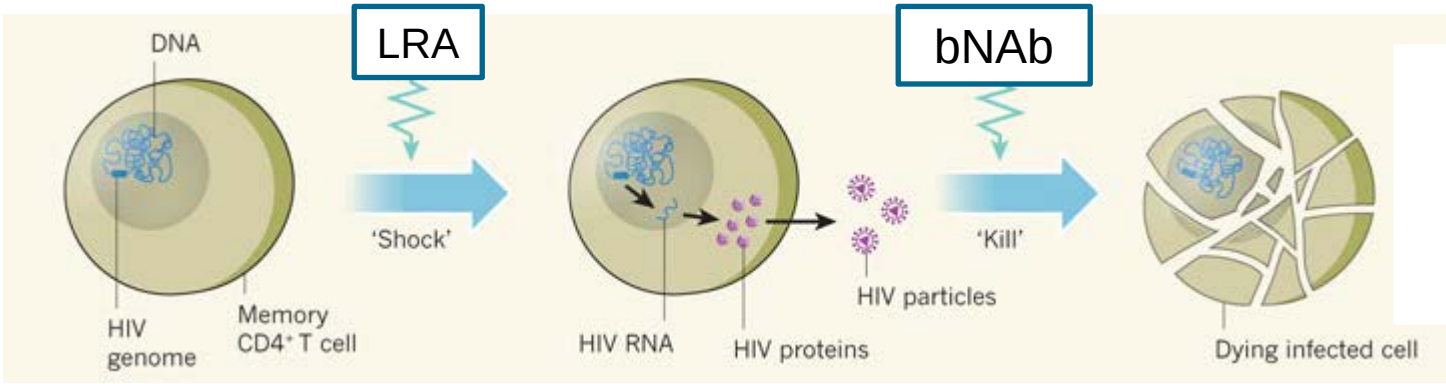
Combination Therapy Trials for Cure

Clinical Investigation and Trial Design

Joseph Eron
Professor of Medicine
UNC Chapel Hill

“Kick and Kill”

- Latency reversing agents (LRAs) activate latent resting and memory T cells, inducing HIV expression and exposing these cells to the immune system
- Enhance clearance of HIV-1 infected cells that are expressing virus or viral proteins (e.g. therapeutic vaccine, anti-exhaustion antibody, modified T-cells, broadly neutralizing or bi-specific antibodies)



Deeks Nature 2012

Decision Points

- What are the criteria for moving interventions into a combination trial?
- Which participants should be studied in combination trials?
- What type of study design should be used to assess combination interventions?
- What endpoints should be used for combination trials?

Choosing a Combination/Study Design

- Demonstration of activity as single agents?
  - Is safety data plus animal/ex vivo data enough?
  - Are there some combinations for which antagonism might be expected?
    - e.g. HDACi affect T cell function, should combining them with vaccines be avoided?
- The timing of administration is likely critical
  - How will this be worked out in advance?
- Are single agent arms necessary?
- Are control arms needed?

Which patients should be studied?

- Acute HIV infection – Treated and Suppressed
  - Pro
    - Small reservoir, limited HIV-1 diversity
    - Preserved HIV specific immunity/more intact innate immune function/less inflammation
  - Con
    - Uncommon population – not scalable
    - May be difficult to “see” an effect without ATI
    - An ATI likely requires a control arm

Which patients should be studied?

- Chronically infected – treated and suppressed
  - Con
    - Viral diversity
    - Difficult to measure relevant reservoir
    - Exhausted HIV specific immunity - ? Less robust innate function
  - Pro
    - Many patients who are interested in participating
    - Potential to measure an impact without ATI
      - What to measure is not clear

Potential laboratory endpoints

- HIV DNA
  - Most DNA is defective, particularly in patients treated during chronic infection. May miss an effect
- CA-HIV RNA
  - RNA transcripts may also be defective
- Cell expressing HIV protein
  - Extremely rare “Needle in a haystack”
- Plasma HIV RNA
  - Can be below limit of detection of most sensitive assays
- Virus outgrowth assay or RNA expression
  - Labor intensive, costly
- Anti-HIV immune responses as a measure of effect

Analytic Treatment Interruption (ATI)

- When should this be the primary endpoint?
- Should the intervention first show an effect on a measure of HIV persistence prior to ATI?
- Endpoint – time to rebound or set point?
- What are the risks of monitored ATI?
- Should control arms undergo ATI?
- Will providers refer participants to MAP studies?

Discussion Questions

- How should we determine sample size?
  - Small studies can only detect large effects
    - Larger effect size – smaller sample but….
  - How do we ensure we don't reject a therapy with a modest benefit just because a study was underpowered to detect the effect?