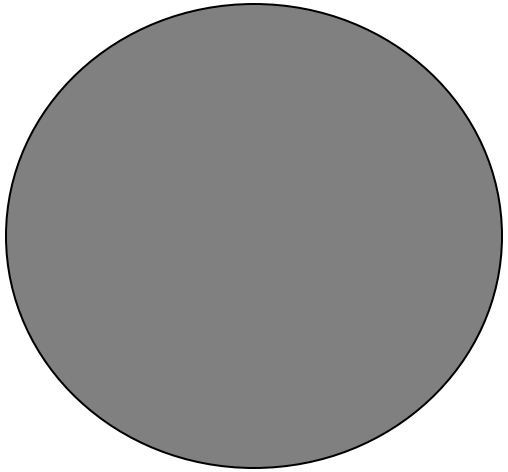
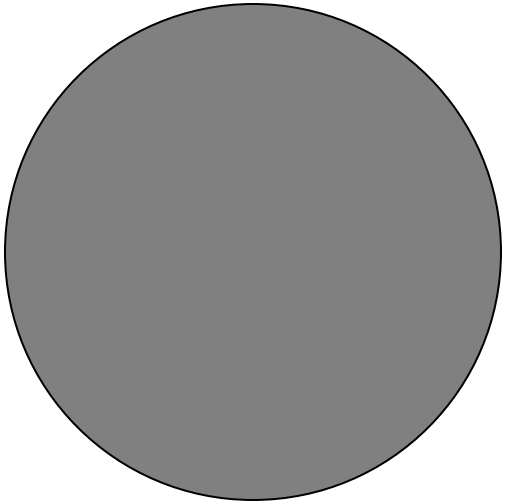
# Not acceptable in salvage trials –

- Enrolling people who can be expected to fail (sacrificial lambs) in order to be assured of getting endpoint events

- Comparator arms that poop out early and inadequately define safety profile





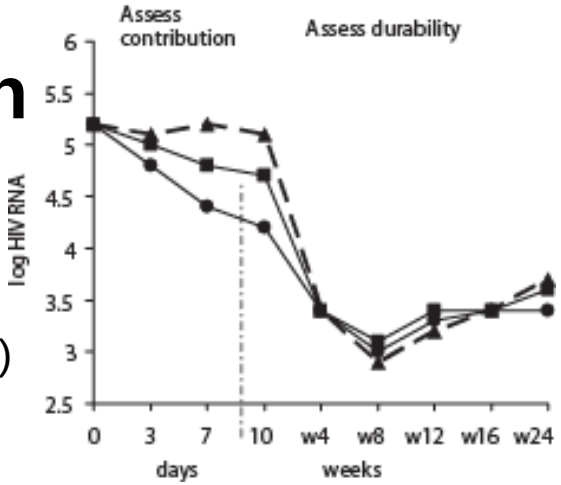
# Proposal A:

## Randomized safety trial - active OBR comparator

- Entry criteria:
  - currently on failing (or intolerable?) regimen
  - two or more active agents in reserve
  - experimental drug expected to be active
- Randomize:
  - Group 1: gets experimental drug plus reserve agents in optimized regimen
  - Group 2: gets reserve agents in optimized regimen
- Outcomes: **comparative safety data**; suppression rates at 24-48 weeks
- Limitations: possible little difference in suppression rates

- Problem:
  - if everyone must be assured suppression, then all participants must have at least two highly active drugs before randomization. But how can you tell if experimental drug contributes to suppression?
- Rely on this trial primarily for safety
  - comparator group remains intact since participants in both groups are suppressed!
  - efficacy data is secondary
    - show lack of antagonism
    - possible contribution to durability; benefit in >100K VL subset?

# Proposal B: single arm trial + lead-in



Struble et al, AIDS 2005

- Entry criteria:
  - currently on failing regimen
  - only **ONE** (or two) active drugs (approved or exp) available in reserve
  - experimental drug expected to be active
- Randomize:
  - Group 1: takes experimental drug for 7-14 days as monotherapy then begins new optimized regimen
  - Group 2: continues failing regimen for 7-14 days then begins new optimized regimen
- Outcomes:
  - show comparative activity in 7-14 days;
  - show suppression rates at 24 weeks in previously unsuppressed, historically hard-to-treat population
- Limitations: minimal comparative safety data

# Approval based on A + B

- *Neither trial is adequate alone: it takes two*
- randomized comparison (A) best demonstrates safety; efficacy data is a bonus
- single-arm study (B) demonstrates durability versus historical expectations for the population (with support from randomized lead-in); observational safety data
  - Randomized dose comparison data from Phase II contributes
- Together they provide complementary data adequate for approval of new drug for salvage indication
- All participants treated; none sacrificed to produce events
- **Viable development pathway for niche drugs that would otherwise not be developed?**