Issues in the design of HIV salvage trials

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Outline

- Study Endpoint
- Definition of Treatment Experienced
- Study Design Issues/Control Arm
- Study Duration
- Statistical Issues

Challenges to developing new therapies for salvage trials (AIDS 2005, 19:747-756)

- 1) Heterogeneity of study participants.
- 2) Evolving definition of a treatment-experienced patient.
- 3) Definitions of clinically relevant and achievable endpoints.
- 4) Early determination of effect of baseline genotype and phenotype for new investigational agents.
- 5) Identification of acceptable comparator regimens (optimized background regimen, OBR).
- 6) Complex efficacy and safety assessments due to cross-over options for participants who experience virologic failure.

Primary study endpoint should reflect treatment goals

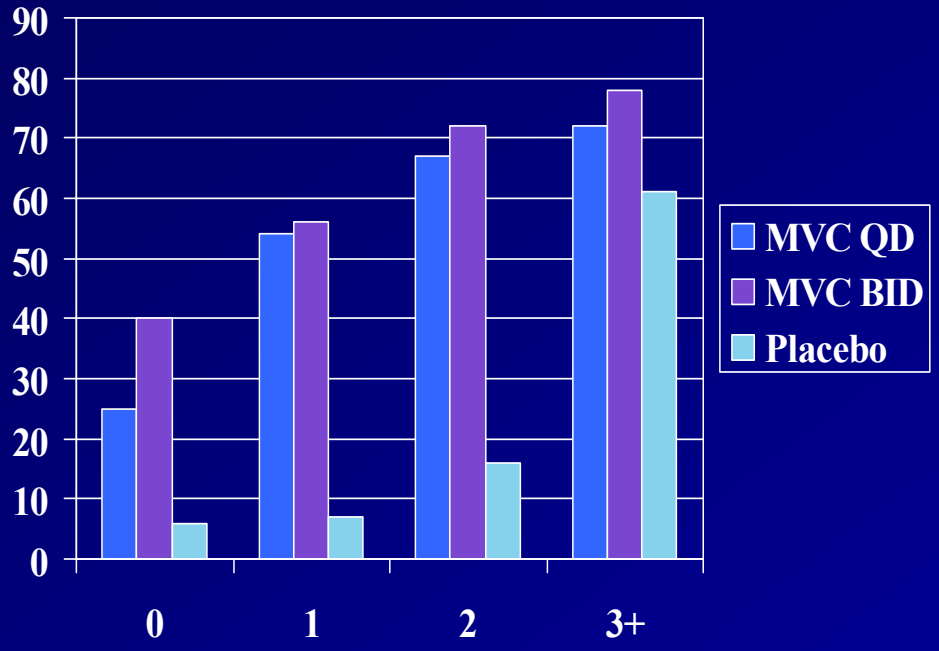
- Goal: maximal virologic suppression (HIV-RNA < 50 copies/mL) in treatment-experienced patients:
  - Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents - December 1, 2007.
  - Treatment for adult HIV infection: 2006 recommendations of the International AIDS Society--USA panel. (Hammer S et al. JAMA. 2006 Aug 16;296(7):827-43.)

Proposed definition of treatment experienced patient

- Two or more fully susceptible ARVs in the OBR.
- One or no fully susceptible ARVs in the OBR.

Response rate (< 400 copies/mL) by susceptibility scores

Maraviroc



Raltegravir

	Raltegravir N=462	Placebo N=237
PSS of OBT		
0	31/67 (46)	1/44 (2)
1	84/145 (58)	22/71 (31)
2	101/142 (71)	26/66 (39)
≥ 3	60/85 (71)	28/48 (58)

Study Designs

Patients with 2 or more fully susceptible ARVs in OBR

Options

- Superiority
  - New agent vs placebo when added to optimized background therapy
- Non-inferiority
  - In class comparison
    - Maraviroc vs investigational CCR5 agent
  - Across class comparison
    - Raltegravir vs investigational entry inhibitor
- Other designs – dose comparisons

Challenges

- Investigational agent + OBR vs Placebo + OBR
  - Issues: Patients with only 2 fully susceptible ARVs in the OBR:
    - Easier to demonstrate superiority for 3 susceptible agents in regimen vs control of 2 susceptible agents
    - Ethical concerns and patient/investigator acceptability of design
    - Study design may need cross-over option for patients who develop virologic failure and complicates safety analysis

Challenges

- In class and cross class comparisons
  - Appropriate study duration to establish efficacy
  - Need to establish non-inferiority margin in patient population
  - Could be difficult to establish magnitude of treatment effect of investigational agent
- Appropriate duration to establish safety and efficacy unknown (e.g. 24 or 48+ weeks)

Background regimen

- Optimized background regimen
  - Mandate at least 2 fully susceptible agents, including all available expanded access agents
- Fixed background regimen
  - Example
    - Darunavir/ritonavir + etravirine + raltegravir
    - Darunavir/ritonavir + etravirine + investigational integrase inhibitor

Study Designs

Patients with

1 or no fully susceptible ARV in OBR

Patients with 1 or no fully susceptible ARV in OBR

- May not be appropriate for randomized clinical trials
- Options
  - Expanded access
  - Open-label safety studies
  - Open-label, non-comparative studies
  - Single-arm design (investigational agent + OBR) with comparison to historical controls.

Issues

- Pros:
  - Provides access to patients with advanced disease
  - Can collect important information on safety, resistance assessment
  - Studies can be conducted in parallel with phase 3 or earlier
- Cons:
  - Only subset may benefit (those with 1 susceptible agent)
  - Functional monotherapy, develop resistance to investigational agent
  - Challenges to interpreting data from historical controls
- Risk/benefit assessment for individual patient
  - Those who can wait for another susceptible agent versus those who cannot wait

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