Statistical Issues: Studies for Treatment-Experienced Subjects

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Basic Principles

- 1) Studies must be designed to minimize the risk of participants receiving only one active drug.
- 2) New drugs must be developed in conjunction with other new or existing drugs to create potent regimens; relevant information about how best to combine drugs should be developed early in phase II investigations.
- 3) Participants should be maintained on assigned regimens long enough to provide reliable comparisons of toxicity between the new and standard treatments.
- 4) When cross over to the new regimen is allowed, appropriate methods must be used to adjust for the resulting informative censoring

Principles Cont.

- **5) Appropriate methods are also needed to adjust for uncontrolled use of potent drugs.**
- **6) Primary endpoint should be viral suppression below levels of detection.**
- **7) Drug efficacy depends on HIV genotype: studies must provide adequate information for classifying future patients according to their predicted response to therapy.**
- **8) Regulatory policy must be modified to assure proper review of drugs that are targeted to patients according to genotype of the infecting agents.**

- DeGruttola V, Flexner C, Schapiro J, Hughes M, van der Laan M, Kuritzkes D, Drug Development Strategies for Salvage Therapy: Conflicts and Solutions. ARHR, 2006

Salvage Studies of Policy Questions
Example: A5241

- Study Question: Probability of achieving treatment success from a new regimen of active agents with cPSS>2.0 not including NRTIs, will not be inferior to that including NRTIs. Endpoint is time to first of virological failure or abandonment of the randomized strategy

Salvage Studies
Efficacy of individual drugs.

Basic Design OBR vs OBR + new drug

Crossover to new drug at virological failure generally permitted. Examples:

- Tipranivir: RESIST endpoint was confirmed 1 log10 or greater decrease plasma HIV RNA at 48 weeks.
- Enfuvitide: TORO endpoint was HIV RNA at 24 weeks.
- Maraviroc: MOTIVATE endpoints change in viral load from baseline to week 24.

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Problems with these designs

- 1) Participants with no active drugs in the OBR assigned to the new drug, or with 1 active drug assigned to placebo, may be essentially receiving monotherapy. Such participants are at high risk of treatment failure and development of additional resistance.
- 2) Rapid cross over to the new drug prevents longer-term toxicity comparisons.
- 3) Differential use of potent drugs other than the study drug may induce a bias in favor of the new drug, especially in unblinded studies

Alternatives to RESIST

- Participants whose only active drug is ENF are randomized to:

  TPV + ENF vs SOC without ENF

- Those with an active drug in addition to ENF are randomized to:

  TPV +OBR vs SOC (can include ENF)

- Patients with no active drug (refuse or resistant to ENF) are either excluded from participation or randomized to:

  TPV+OBR vs SOC.

Advantages:

- No participant willing to take ENF gets effective monotherapy
- Endpoint can be viral suppression below detection.
- Impact of TPV alone on toxicity and efficacy can be evaluated among participants who refuse ENF.
- TPV studied in combination with ENF among patients for whom this use of TPV may be optimal. (We can replace ENF in this example with any drug never before seen by the patient population, whether new or not.)
- Studying one drug only in combination with another may not be optimal from the perspective of drug development, it may best meet the interest of potential study participants.

Modifications

- Lederman, Miller, Weller and Deeks proposed: single arm study in which all patients get "optimal therapy." and change in VL is the endpoint. Compare with historical controls.

- For patients with 2 active drugs, including new drug: randomize to:

  2 active old drugs vs. 1 + new drug

  (similar to DFSHVK, 2006).

Table: Examples of ranges of complete virological responses to salvage regimens that included two active drugs in combination with a background of recycled partly effective agents.

	A	B	C	D
A	X	78–80%	80–85%	70–75%
B	78–80%	X	86–90%	65–70%
C	80–85%	86–90%	X	72–80%
D	70–75%	65–70%	72–80%	X

Lederman et al.: “…when agent A was combined with either agents B, C or D, the response rates ranged between 70 and 85%. Therefore for trials of the new agent E, ranges of complete responses when used in combination with these other active agents should be between 70 and 85%. A failure to achieve such a response would suggest that the experimental agent is not as active as the other agents commonly used in patients with multidrug-resistant HIV. In that instance, additional studies would be necessary to define what role if any this drug might have as a component of salvage therapy.”

Confounding

- Confounding is a major issue in using historical controls.
- Also, in randomized studies, potent drugs may be added or withheld from regimens because of events that occur post –randomization.
- Example: In RESIST, the choice of using ENF may have been impacted by the treatment arm to which a patient was randomized and the desire to avoid effective monotherapy.
- In general, we refer to ancillary treatment choice that is affected by personal characteristics as “confounding by indication (CBI).”

Adjustment for CBI
Example ENF use in RESIST

- 1) Estimate the probability that a study participant used ENF, given his/her personal characteristics;
- 2) Regress the study endpoints on treatment and patient characteristics.
- 3) Combine these analyses to estimate the TPV effect. (Need sufficient number of patients with and without ENF in both arms.)
- Methods for reducing dependency of model assumptions, and to analyze sensitivity to unmeasured confounding factors are also available.
- Post-hoc stratification by ENF use is NOT valid either for testing or for estimation.

Causal Methods

Other applications of such causal methods:

1) comparing toxicities between arms, in the presence of early cross-over to the new treatments.

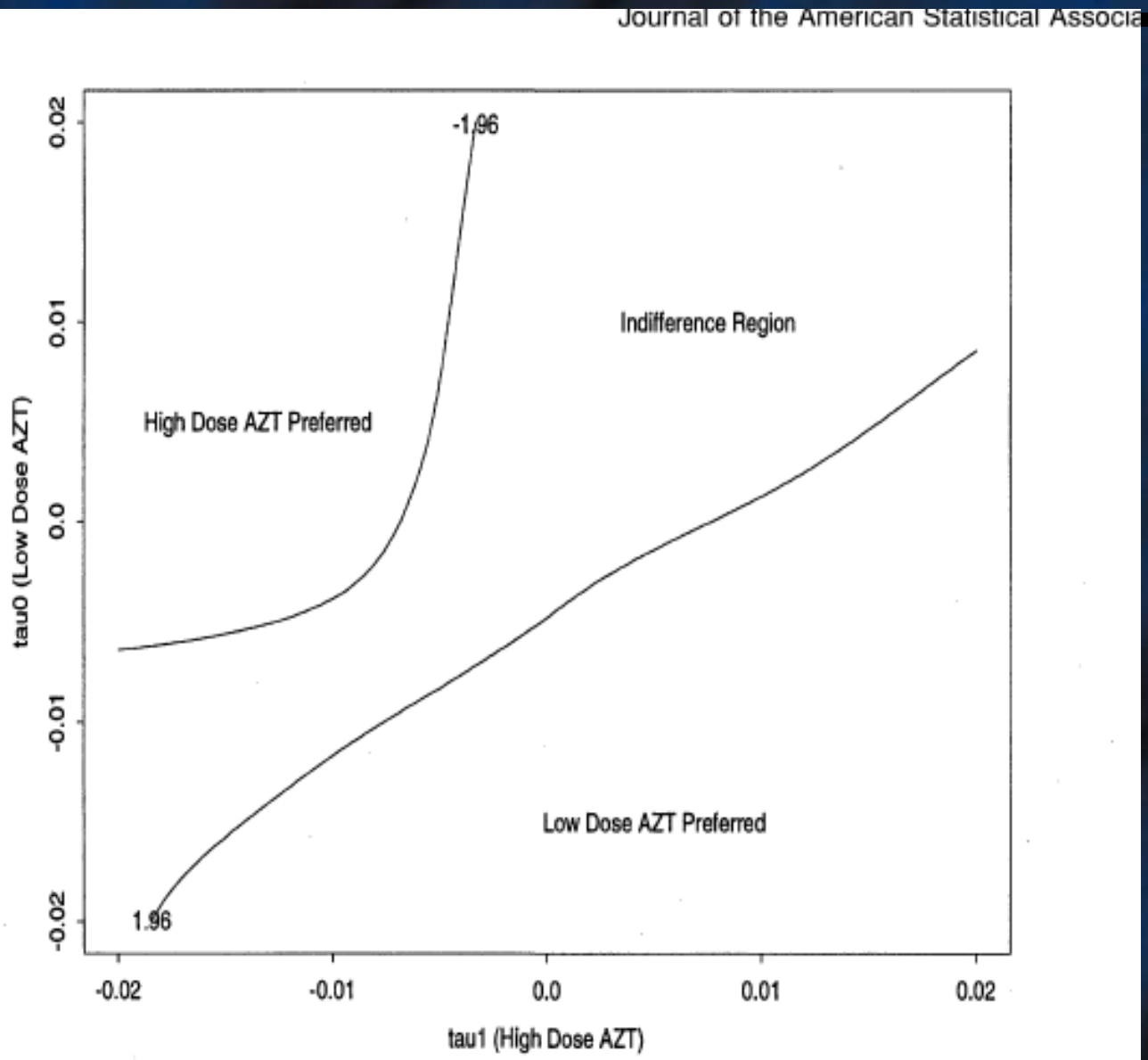
2) adjustment for losses to follow-up.

3) adjustment for confounding in use of historical controls?

Example of sensitivity analysis

- Investigation of impact of high vs low dose AZT monotherapy on week 32 CD4 in ACTG 002.
- What is the sensitivity of results to assumptions about dropout process.
- Scharfstein, Robins, Rotnitzky JASA 1998

Sensitivity Analysis



Tau = .01 implies patients with CD4=200 at week 32 are 2.7 times more likely to be missing week 32 CD4 than those with CD4=100.

Identifying Target Populations

- The proliferation of new drugs and new classes will lead to ever more complex patterns of resistance.
- Can we establish a general principle to guide therapy? e.g. 2 active drugs from 2 classes (with or without recycled drugs); cPSS or cGSS > 2.
- Predicting Rx response from genotype is essential.
- In addition, predicting toxicity as well as efficacy is essential to balance cost and benefit.

Challenges

- Simple prediction rules for efficacy and toxicity may be possible (e.g. counting number of resistance mutations may be misleading).
- Impact of resistance mutations may depend on presence of others (e.g. impact of mutation at site PR 46 on IC50 for amprenavir depends on presence of mutation at PR 88).
- Mutations that cause resistance to one drug may hypersensitize to another (some ZDV mutations hypersensitize to EFV).

To develop relevant information, we need:

- Large databases to use as a basis for predicting cost and benefit at the individual patient level.
- Methods for handling high dimensional predictors (HIV genotype, SNPs, lab tests)
- Causal methods for handling informative dropout, CBI, cross-over.

Example: Forum Project on Standardization And Clinical Relevance of HIV Resistance Testing

Collected data on a variety of studies of abacavir: ACTG 364, 372, ARCA, Homer Cohort, EuroSIDA, CNA-GSK, I.Co.N.A., JAGUAR, NARVAL, Swiss HIV Cohort, Stanford HIV Resistance Database, University Sacro Cuore, UK Resistance Database, RDI, I.Co.N.A, Stanford, EuroSIDA

Forum Project: Resistance to Abacabir

Pattern	μ‡j	N	NP	SP
1 1 1 1 1	-0.80/-0.57	23	0.020	0.022
1 1 1 1 0	-0.85/-0.61	29	0.050	0.020
1 1 0 1 1	-0.89/-0.64	47	0.030	0.007
1 1 0 0 1	-1.04/-0.85	48	-	0.083
1 0 0 1 1	-1.06/-0.80	29	-	-
1 1 0 1 0	-1.14/-0.96	32	-	-
1 0 1 0 1	-1.27/-1.03	15	-	-
1 1 1 0 0	-1.30/-1.03	18	-	-
1 0 1 1 1	-1.37/-1.11	14	-	-
1 0 1 1 0	-1.41/-1.10	50	-	-
1 1 1 0 1	-1.44/-1.20	36	-	-
0 1 1 1 0	-1.48/-1.19	45	-	-
0 0 0 0 0	-1.54/-1.31	110		

† Patterns are determined by RT codons (41 67 135 184 210), 1:mutation, 0:wild type.

‡ Mean response unadjusted/adjusted for covariate.

Conclusions

- Studies providing one active drug by design belong in the ACTG 002 era.
- Drugs need to be developed in combination
- Large databases are needed to assess cost-benefit at individual level.
- Modern methods must be used to adjust for CBI, dropout, cross-over as well as high-dimensional predictors