Forum for Collaborative HIV Research

Overview of GSS and PSS Scores

Rethinking Clinical Trial Designs Roundtable

Veronica Miller, PhD

Acknowledgements

- Members of the Standardization and Clinical Relevance of HIV Drug Resistance Testing Working Group

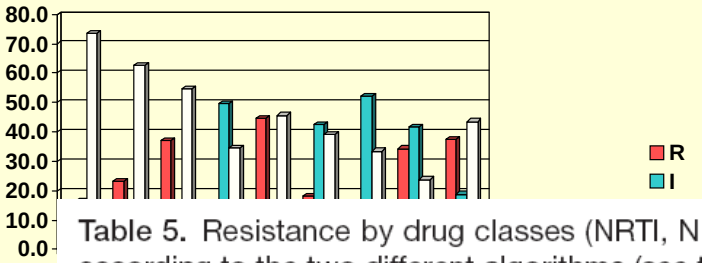
Overview

- Calculation of GSS & PSS scores has not been standardized
  - Historically, a simple 1/0* system applied to re-analysis of 12 studies (DeGruttola et al 2000)
- Request by the FDA to review approaches & issues
- Many of the issues may not be easily resolved
- Translation of GSS and PSS scores:
  - "number of active drugs available"
  - Realistic/feasible background regimen

*1.5/0.75 for special cases

Test Interpretation and Classification of Drugs

Level of resistance to abacavir according to system



Costagliola 2006

Table 5. Resistance by drug classes (NRTI, NNRTI, PI, fusion inhibitor) for the 130 randomized patients according to the two different algorithms (see text for definition 1 and 2)

	VIRCO	Stanford Definition 1	Stanford Definition 2
	n (%)	*n* (%)	*n* (%)
Patients not resistant to any class	3 (2.3)	1 (0.8)	2 (1.5)
Patients resistant to one class	10 (7.7)	8 (6.2)	10 (7.7)
Patients resistant to two classes	45 (34.6)	37 (28.5)	38 (29.2)
Patients resistant to three classes	72 (55.4)	84 (64.6)	80 (61.5)
Patients resistant to four classes	0 (0)	0 (0)	0 (0)

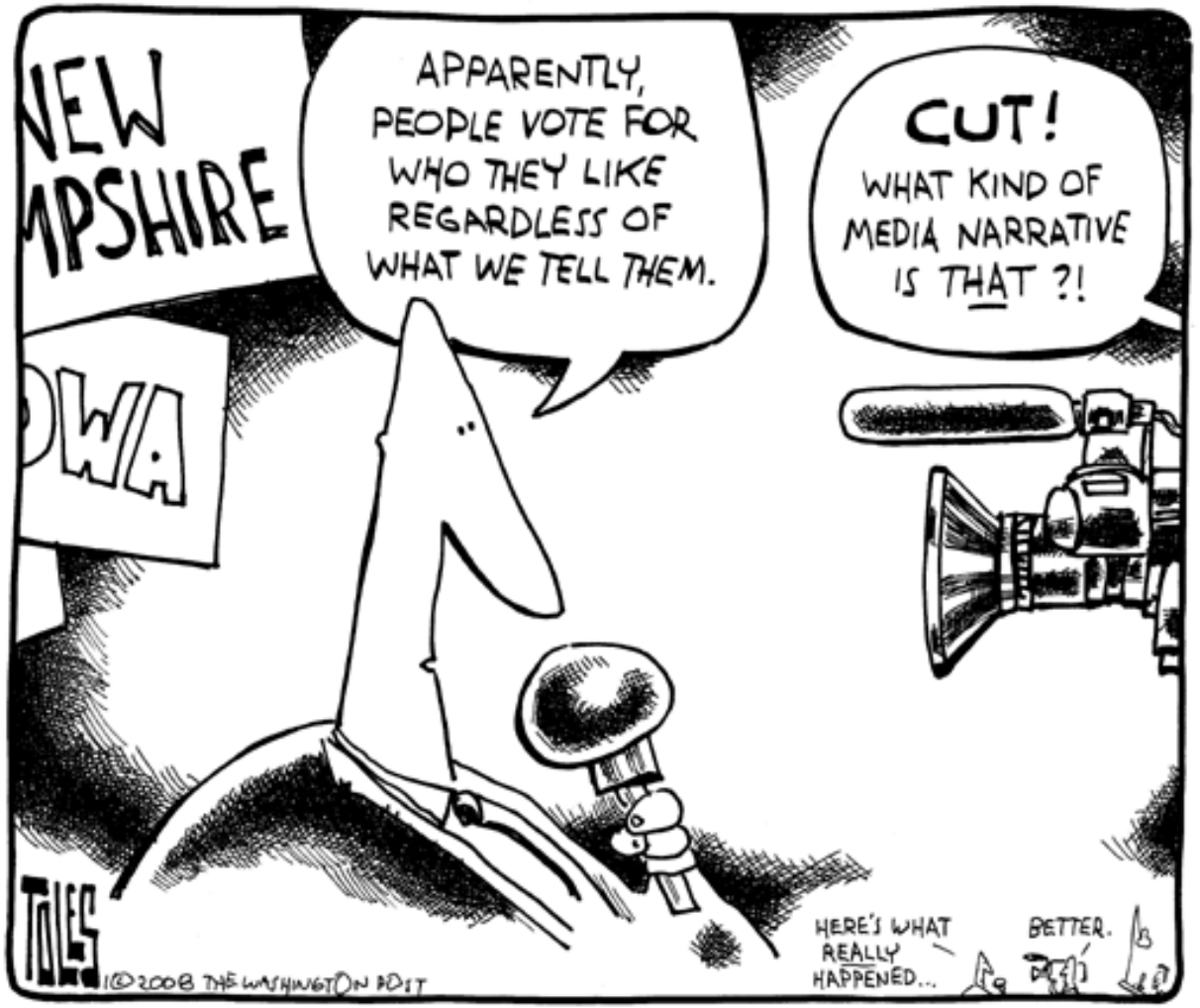
Desai 2007

Q1: Does more effort need to be placed into standardizing classification of drug activity for clinical trial design and analysis?

Available Active Drugs vs. Feasible Background Regimen

- Optimization includes tolerability of drug
- Patients may not be able to use all the active drugs that are by GSS or PSS definition available to them
- Restriction in combining drugs

People don't chose what they are told to chose



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Available Active Drugs vs. Feasible Background Regimen

- Optimization includes tolerability of drug
- Patients may not be able to use all the active drugs that are by GSS or PSS definition available to them
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Q2: Should the patient definition for inclusion into trials be modified to reflect the potential to build a feasible regimen?

Resistance Test is a Snapshot

- Resistance profiles change depending on whether patient is on or off drug
- Complete and accurate treatment history needed
  - Treatment guidelines recommend basing regimen on resistance test and treatment history

Q3: Should GSS & PSS scores include historical resistance test results? What additional research is needed?

Q4: Should GSS & PSS scores be modified by treatment history? Or treatment history separate category for 'number of active drugs'?

Q5: Should GSS & PSS scores be modified according to whether a drug was previously used?

Resistance Test is a Snapshot

- Role of minority variants
  - Clinical relevance in sd nevirapine pMTCT studies
  - Adult studies (e.g. Mellors et al 2004)
  - Newer technology increasingly available

Q6: To what extent should more sensitive resistance test methods be used? What additional research is needed?

Class Specific Issues

- Potency of different drugs
  - Weight scores based on viral load decline in monotherapy studies?
- Previous use of drugs vs. resistance testing
  - E.g. enfuvirtide yes/no; naïve yes/no
- CCR5 antagonists and tropism
  - X5 only or X5/X4 mixed/dual?

Q7: Should scores differentiate between drugs with higher or lower potentcy ?

Q8: Score some drugs simply on basis of prior use?

Q9: Include baseline tropism if CCR5 antagonists used?

Class Specific Issues

- Residual/intermediate activity
  - Some drugs contribute even though classified as ‘not active’
  - Continuum vs. all or nothing: what to do with the middle ranges?

Table 2 Number of active drugs started with abacavir (new or recycled, abacavir excluded) according to the Rega, Stanford and Agence Nationale de Recherches sur le Sida (ANRS) interpretation systems

	Interpretation system		
No. of active drugs besides abacavir	Rega 6.4 [*n* (%)]	ANRS V13 [*n* (%)]	Stanford 1.4.8 [*n* (%)]
0	424 (32)	542 (42)	445 (34)
0.5	75 (6)	21 (2)	88 (7)
1	267 (20)	445 (34)	289 (22)
1.5	155 (12)	43 (3)	163 (12)
2	202 (15)	214 (16)	178 (14)
2.5	52 (4)	7 (1)	50 (4)
3	112 (9)	30 (2)	79 (6)
3.5	8 (0.6)	0 (0)	6 (0.5)
4	8 (0.6)	3 (0.2)	4 (0.3)
4.5	0 (0)	0 (0)	2 (0.2)
5	2 (0.2)	1 (0.1)	2 (0.2)
5.5	1 (0.1)	0 (0)	0 (0)

Cozzi-Lepri 2008

Class Specific Issues

- Residual/intermediate activity
  - Some drugs contribute even though classified as ‘not active’
  - Continuum vs. all or nothing: what to do with the middle ranges?

Q10: What are the best ways to score drugs with intermediate activity?

Mutations that Increase Drug Activity

- Hypersusceptibility demonstrated
  - E.g. M184V for ZDV
  - for NNRTI's if NRTI mutations present
  - protease inhibitors
- Affects virologic response

Q11: How should genotypes that include hypersusceptibility mutations be integrated into GSS score?

Weighted Genotypic Scores

- Scherer et al 2007 for tipranavir
  - Mutations that increase response (<0)
  - Mutations that decrease response (>2)
  - Minor mutations (1-2)
- Virtual phenotype and weighted scores were best predictors for virologic response

Q12: Should weighted scores be developed for mutations associated with all drugs?

Phenotype based on Phenotypic information based Clinical Cut-Offs

- Upper and lower cut-offs
  - E.g. 20% or 80% of drug effect lost (Bacheler 2007)
  - E.g. upper cut-off corresponding to -0.3 log viral load change (Coakley et al)
  - Inclusion of hypersusceptible ranges
    - PIs, NNRTIs: 1.0 if fully active; 1.5 if hypersusceptible
    - NRTI's: 0.5 if fully active; 1.0 if hypersusceptible

Q13: Should phenotypic scores be assigned based on a continuous range?