

A POTENCY WEIGHTED SENSITIVITY SCORE ENABLES A TRANSPARENT AND ACCURATE PREDICTION OF THE ACTIVITY OF A COMBINATION THERAPY

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INTRODUCTION

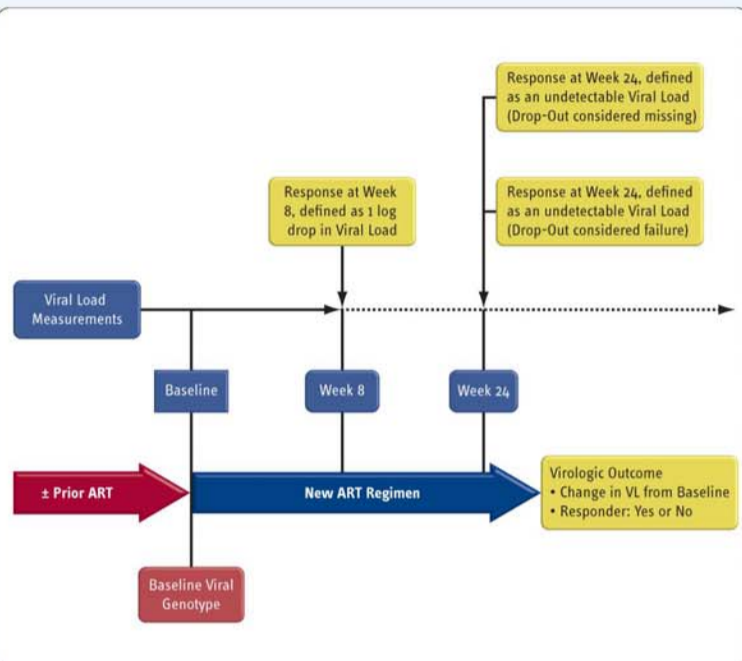
The activity of HAART regimens is often expressed as a phenotypic or genotypic sensitivity score (PSS/GSS): the sum of activities of the drugs in a regimen accounting for viral resistance.

While simple GSS or PSS scores are reasonably good predictors of virologic response to a new HAART regimen, one drawback of this approach is that all drugs are treated as if they have the same potency, while laboratory and clinical evidence suggests that some drugs, and drug classes, are more potent than others.

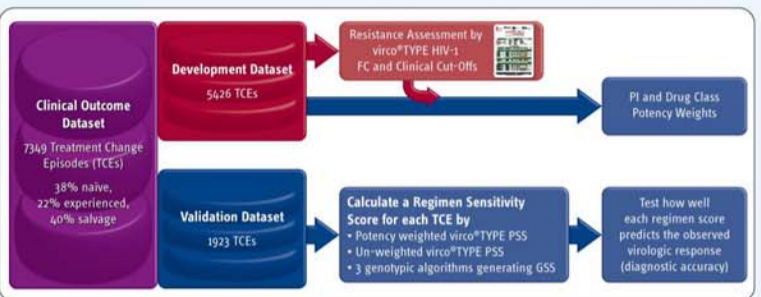
We report here the derivation of weighted sensitivity scores (wPSS) combining drug resistance factors with weights reflecting differences in drug potency.

METHODS

ELEMENTS OF A TREATMENT CHANGE EPISODE



OVERVIEW OF DATA AND ANALYSIS



RESISTANCE ESTIMATES

Resistance factors were assigned using previously derived virco*TYPE HIV-1 clinical cut-off models. The resistance factor for each drug varies from 0 (fully resistant) to 1 (fully sensitive).

Patients defined as naive, experienced and salvage as follows:

- Patients without mutations on the WHO drug resistance surveillance list were classified as naive.
- Patients with mutations were classified as experienced and salvage by a discriminant analysis trained on the genotypes of patients in clinical trials specifically enrolling experienced or salvage patients.

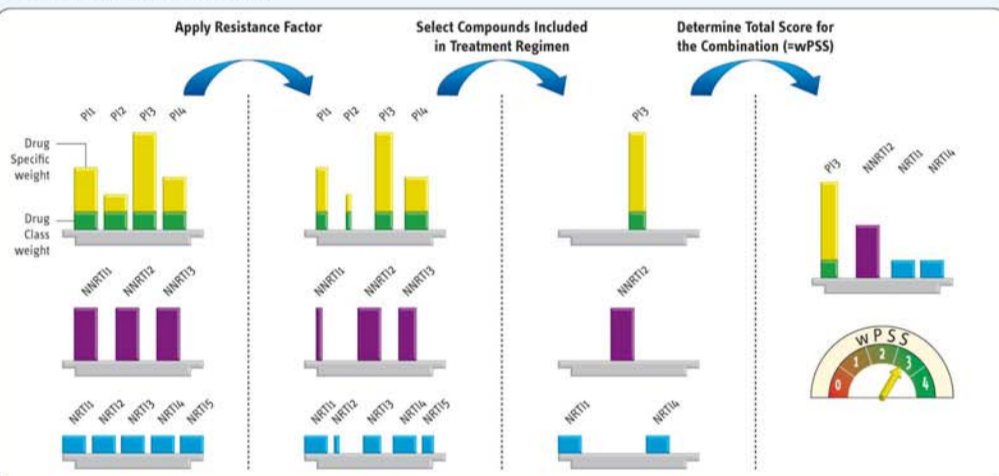
DERIVATION OF POTENCY WEIGHTS

Weights were determined using double robust estimation modeling of the week 8 viral load change. This statistical approach is able to cope with imbalances in the dataset with respect to other patient (baseline viral load), virus (resistance) or treatment characteristics (other drug classes in the regimen) that may affect virologic response and that may be confounded with the drugs to be compared:

- PI drug weights were derived by comparing the response (viral load change at week 8) of patients receiving a particular PI to the response of patients receiving a reference PI (LPV). The LPV weight is fixed at 1.
- Drug class weights were determined by comparing the viral load change in patients taking a particular drug class with patients not taking that drug class.

EVALUATION OF wPSS AND OTHER REGIMEN SCORING APPROACHES AS PREDICTORS OF VIROLOGIC RESPONSE TO A NEW HAART REGIMEN

CALCULATION OF REGIMEN SCORES



Regimen Scores were calculated as the sum of scores for drugs used in the regimen according to the following rules

	Sensitive/Maximal Response	Intermediate/Possible Resistance/Reduced Response	Resistant/Minimal Response
HIVdb	1	0.5	0
ANRS	1	0.5	0
Rega	1 (1.5 if boosted PI)	0.25-0.75 depending on drug class	0
virco*TYPE cPSS	0.8-1.0	0.2-0.8	0-0.2
virco*TYPE wPSS	0.8-1.0 x drug class and PI specific weights	0.2-0.8 x drug class and PI specific weights	0-0.2 x drug class and PI specific weights

RESULTS

DERIVATION OF DRUG WEIGHTS

Drug class weights determined using double robust estimation were 1.0, and 1.1 for NNRTIs and PIs respectively and 0.3 and 1.1 for NRTI components with 1 and ≥2 active NRTIs.

PI specific weights ranging from 0.5 (NFV) to 1.6 (DRV/r BID) were determined using double robust estimation. Table 1 presents individual drug weights and drug class weights.

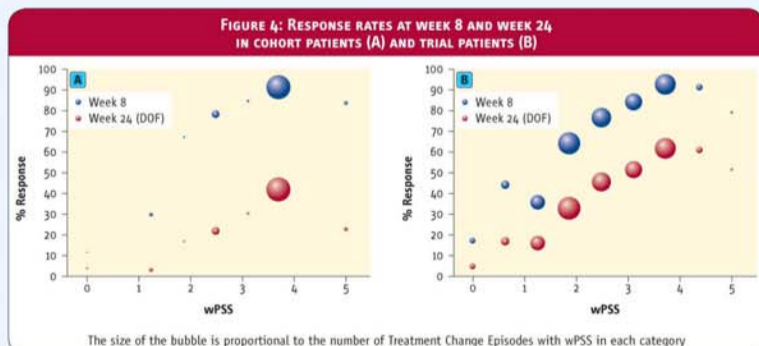
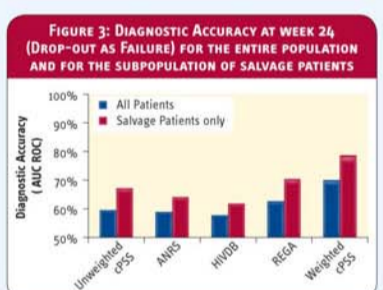
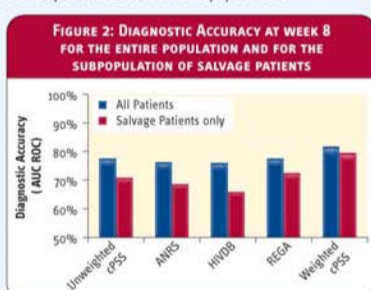
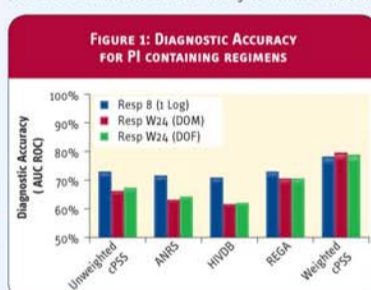
TABLE 1: OVERVIEW OF DRUG WEIGHTS AND DRUG CLASS WEIGHTS

DRUG	WEIGHT
NNRTIs	1.0
PIs	1.1
NRTIs	
1 active	0.3
≥2 active	1.1
Specific PIs	
LPV/r	1.00
NFV	0.54
IDV/r	0.74
ATV/r	1.00
FPV/r	0.69
TPV/r	0.64
DRV/r (800 mg QD)	1.25
DRV/r (600 mg BID)	1.57

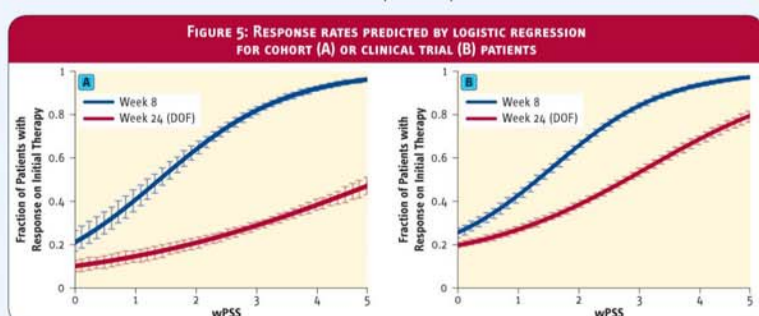
PREDICTION OF VIROLOGIC RESPONSE ON THE UNSEEN VALIDATION DATASET

	DIAGNOSTIC ACCURACY (AREA UNDER THE ROC CURVE)		
	All Regimens	Salvage Regimens	
	>1 log VL decline at week 8	>1 log VL decline at week 8	BQL at week 24 (DO=F)
Potency Weighted PSS	82%	79%	79%
Unweighted PSS	78%	71%	67%
ANRS GSS	76%	69%	64%
HIVdb GSS	76%	66%	62%
Rega (weighted PSS)	78%	72%	70%

FIGURES 1-3 demonstrate the accuracy of the wPSS at different time points and for different populations



- As illustrated in Figure 4, the wPSS is well correlated with virologic response in clinical trials while most patients in the cohort population had a similar wPSS
- Based on Figure 5 the wPSS can be associated with an expected response rate.



- Based on Figure 5 the wPSS can be associated with an expected response rate. Using the "Drop-out as Failures" analysis, the response rate in clinical cohorts at week 24 is reduced because of changes in treatment regimens for reasons other than virologic failure.

CONCLUSIONS

- A potency weighted PSS score was a more robust predictor of response than the unweighted PSS and several GSS.
- The wPSS enables an accurate and transparent evaluation of a combination regimen, with a higher weight for compounds that make a greater contribution to treatment success.
- The probability of treatment success for an individual patient can be predicted by comparing the wPSS to the observed response rate in a population with the same score.

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