

Head to Head Comparison of Widely Used HIV-1 Drug Resistance Algorithms: Retrogram™ and VGI-TRUGENE HIV-1®

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Background

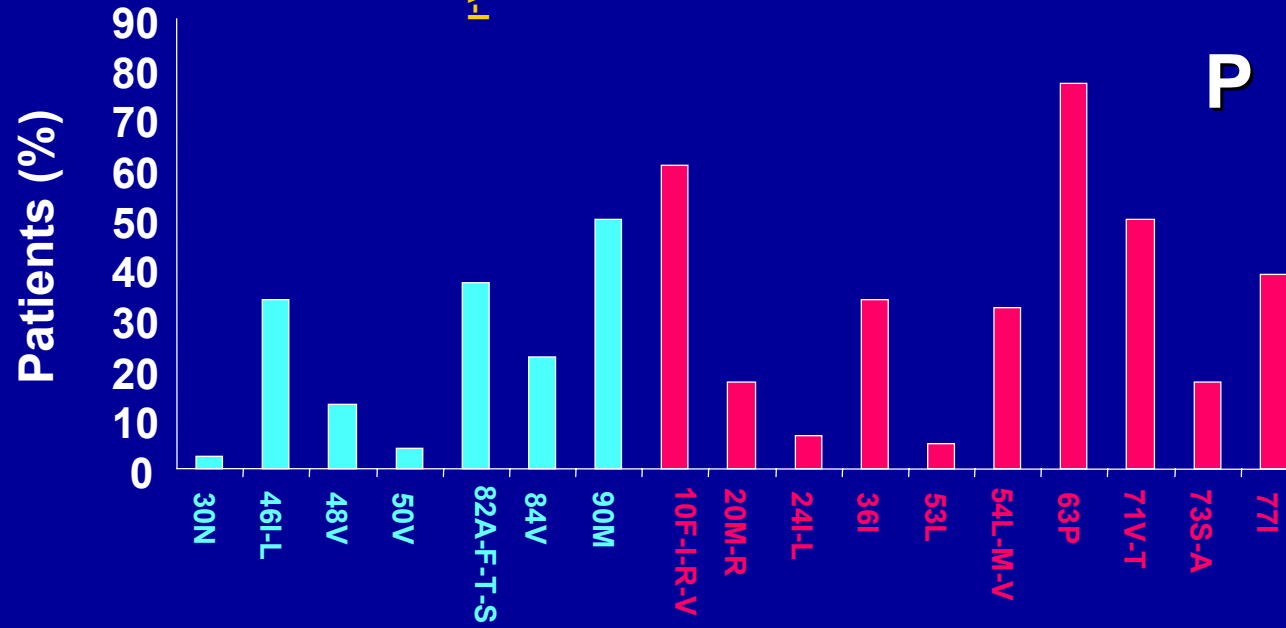
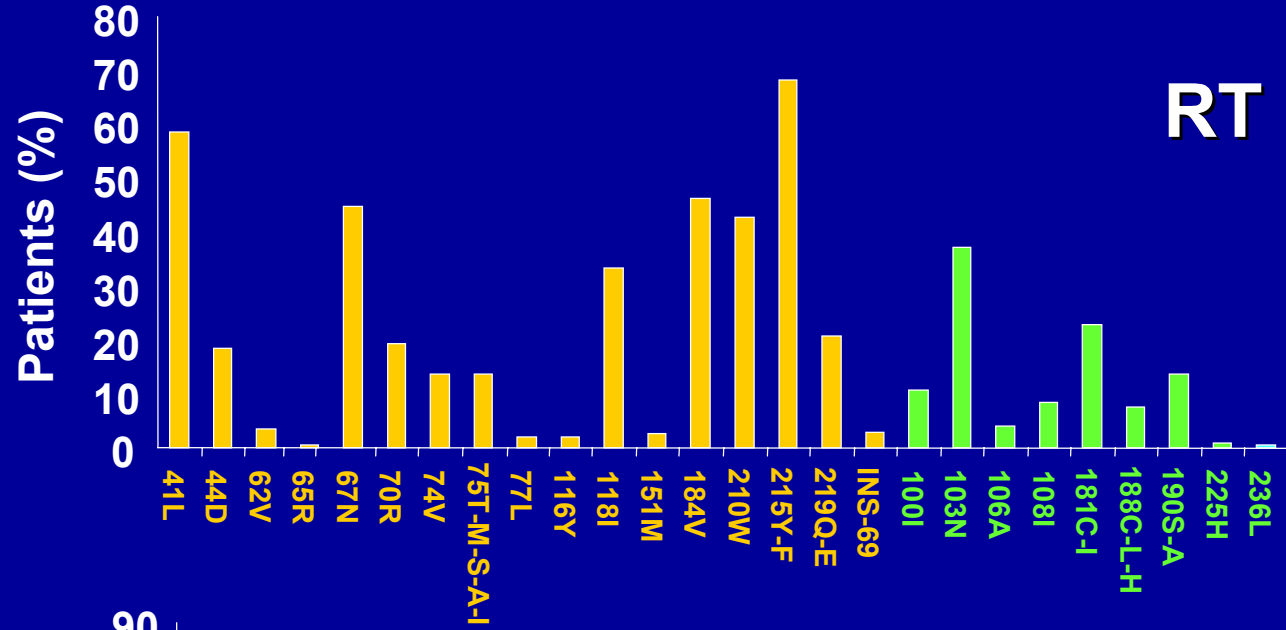
- ✓ As the number of available ARV drugs is growing, interpretation of genotypic resistance patterns is increasingly complex due to the effect of individual mutation on drug susceptibility as well as interactions among different mutations
- ✓ Few data are available to assess concordance across the two genotype interpretation systems most frequently used in Italy (i.e. Retrogram™ and VGI-TRUGENE *HIV-1*®)

Methods I

- ✓ This is an opportunistic analysis nested in the GenPherex study, also presented at this Conference (poster # 589-T)
- ✓ Complete sequences in the HIV reverse transcriptase (RT) and protease (P) genes of 201 patients have been performed by Virco, Mechelen, Belgium
- ✓ Substitutions from the wild-type reference strain HXB2 have been reported
- ✓ Among these substitutions, those recognised by the *International AIDS Society (HIV Clin Trials, April 2001)* as resistance related have been described

Results I

Prevalence of resistance mutations



Methods II

- ✓ Any substitutions from the reference strain HXB2 have been entered into RetroGram 1.4™ and VGI-TRUGENE HIV-1® (Guidelines 3.0; vl.15)
- ✓ Concordance of both Retrogram and VGI interpretation outputs was investigated by the kappa measure of interrater agreement ranked into 5 classes, with kappa ≥ 0.4 considered significant for agreement
- ✓ Two complementary output normalisations were considered for the comparison as shown below:

1)

Retrogram	VGI
A	S
B	PR
C+D	R

2)

Retrogram	VGI
A+B	S
C+D	PR+R

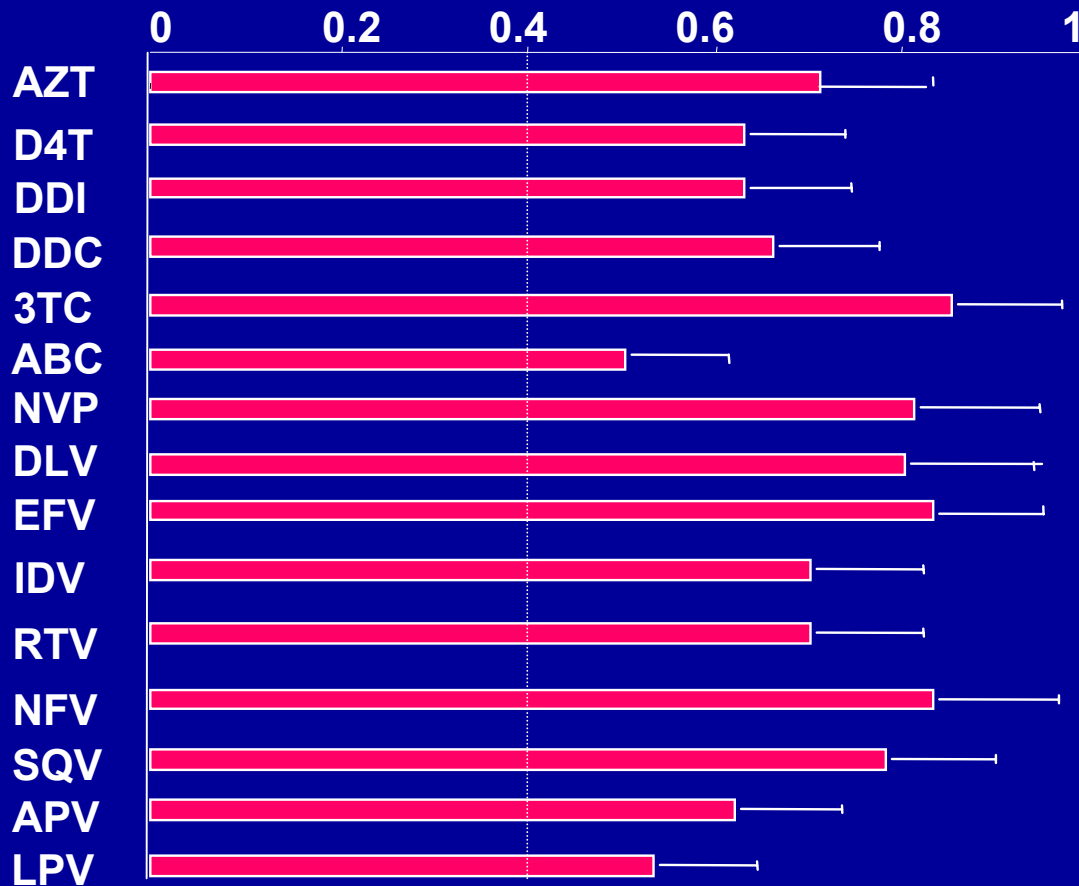
Retrogram: class A = “can be used; class B = “consider use if no class A drug available”; class C = “consider use if no class A or B drugs available; class D = “consider use if no class A, B or C drug available”

VGI: class S = “no evidence of resistance”; class PR = “possible resistance”; class R = “resistance”

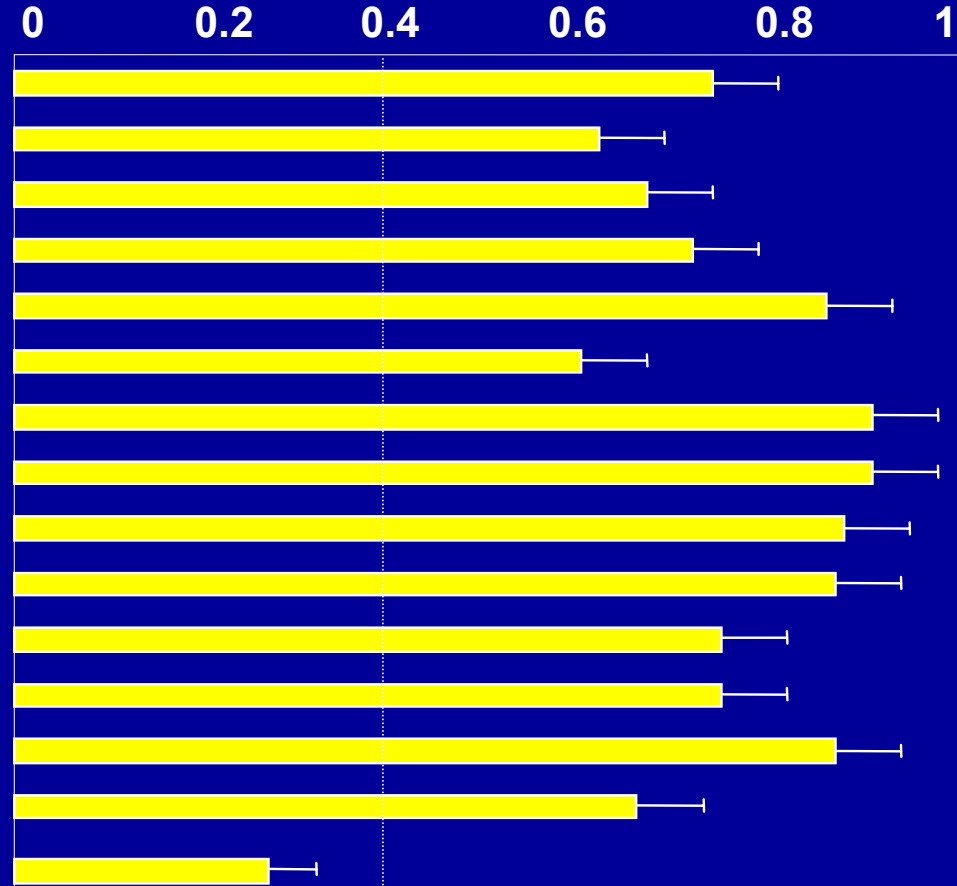
Results II

Kappa agreement

1st output normalization



2nd output normalization



Methods III

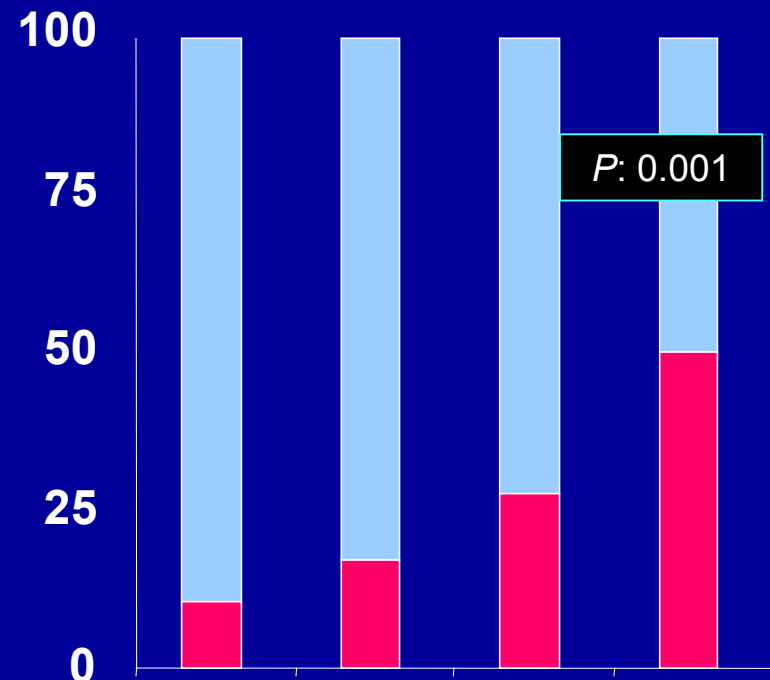
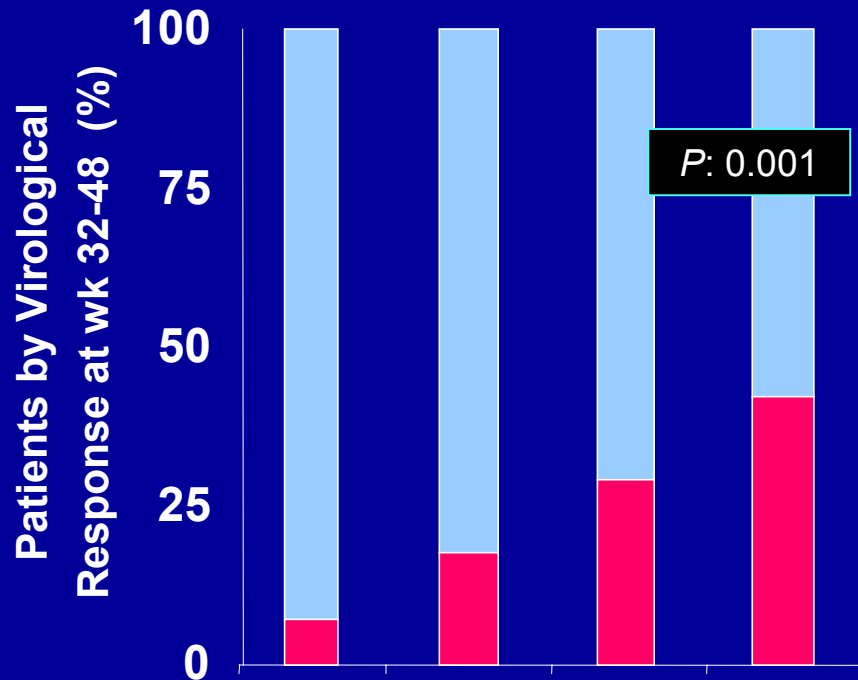
- ✓ To assess the correlation with the virological outcome, resistance was categorized by sensitivity scores
- ✓ A score of 1 was assigned for each sensitive drug in the salvage regimen (except for ritonavir which was always used as baby-dose) either with RetroGram (class A) or with VGI (class S). On the contrary, 0 value was attributed in case of any degree of resistance
- ✓ Association of the sensitivity scores of the prescribed regimens and treatment response (HIV-RNA <400 copies/ml at week 32 and/or 48) was studied in patients who started therapy (n: 173)
- ✓ A multivariate analysis was performed including all the independent variables as follows: sensitivity score, study arm (real vs. virtual phenotype used to decide therapy), baseline CD4, baseline viral load and adherence (scored in 3 classes: <50%, 50-80%, >80% missed doses during the week before week 32)
- ✓ The importance of treatment history was then tested in a separate model

Results III

Sensitivity score vs. Virological response (ITT)

■ Detectable

■ Undetectable



Systems

TRUGENE HIV-1™

RetroGram 1.4®

Score

0

1

2

3-4

0

1

2

3-4

Predictors of Virological Outcome

Multivariate Models -- VGI

Covariates	O.R.	95% C.I.	P
Arms	0.86	0.34-2.17	0.746
BL CD4/mm ³	3.44	1.19-10.0	0.023
BL Log ₁₀ HIV-RNA	2.70	0.99- 7.34	0.052
Adherence W32	0.37	0.16-0.85	0.019
Sensitivity score *	2.21	1.48-3.32	<0.0001
Arms	0.84	0.35-2.0	0.703
BL CD4/mm ³	3.80	1.41-10.28	0.008
BL Log ₁₀ HIV-RNA	2.37	0.94- 5.97	0.068
Adherence W32	0.37	0.17-0.79	0.10
Number of new and sensitive drugs *	3.01	1.33-6.81	0.008

* As these covariates are intrinsically correlated, they have been tested in two separate models

Predictors of Virological Outcome

Multivariate Models -- RetroGram

Covariates	O.R.	95% C.I.	P
Arms	1.18	0.49-2.85	0.705
BL CD4/mm ³	2.90	1.07-7.82	0.036
BL Log ₁₀ HIV-RNA	1.99	0.78- 5.04	0.149
Adherence W32	0.35	0.16-0.77	0.009
Sensitivity score *	2.15	1.40-3.32	<0.0001
Arms	0.83	0.34-1.99	0.672
BL CD4/mm ³	3.80	1.37-10.57	0.010
BL Log ₁₀ HIV-RNA	2.41	0.94- 6.21	0.068
Adherence W32	0.37	0.17-0.80	0.011
Number of new and sensitive drugs *	5.27	2.0-13.93	0.001

* As these covariates are intrinsically correlated, they have been tested in two separate models

Conclusions

- ✓ **Output interpretations did not differ significantly between RetroGram 1.4 and VGI-TRUGENE *HIV-1* (Guidelines 3.0, v1.15) in our cohort of heavily pretreated patients and this provides initial cross-validation**
- ✓ **Agreement was moderate for the drugs most recently introduced into clinical practice, probably reflecting limited knowledge of their resistance patterns**
- ✓ **Resistance results with both systems were similar and powerful predictors of virological response in the long-term follow-up**
- ✓ **Notwithstanding, adherence and baseline CD4 cell count were also independently associated with treatment response**

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