

Real vs. Virtual Phenotype:

12-month Results from the GenPherex Study

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Background

- ✓ HIV-1 drug resistance tests have been proven beneficial for the virological outcome. Although this benefit has not been invariably reported, guidelines have given sound recommendations toward the use of such testing after virological failure
- ✓ Genotypic tests are easier to perform but resistance pattern interpretations may be difficult. By contrast, phenotypic tests provide a more direct measure of HIV-1 drug susceptibility but they are expensive, time consuming, particular expertise and special laboratories are needed, and clinical cut-offs to interpret results are still undefined for most of the drugs
- ✓ In an attempt to overcome drawbacks of the two methods, Virco has developed the virtual phenotype (v-PHT) as an alternative way to interpret a genotype, but this has not been compared in RCT's

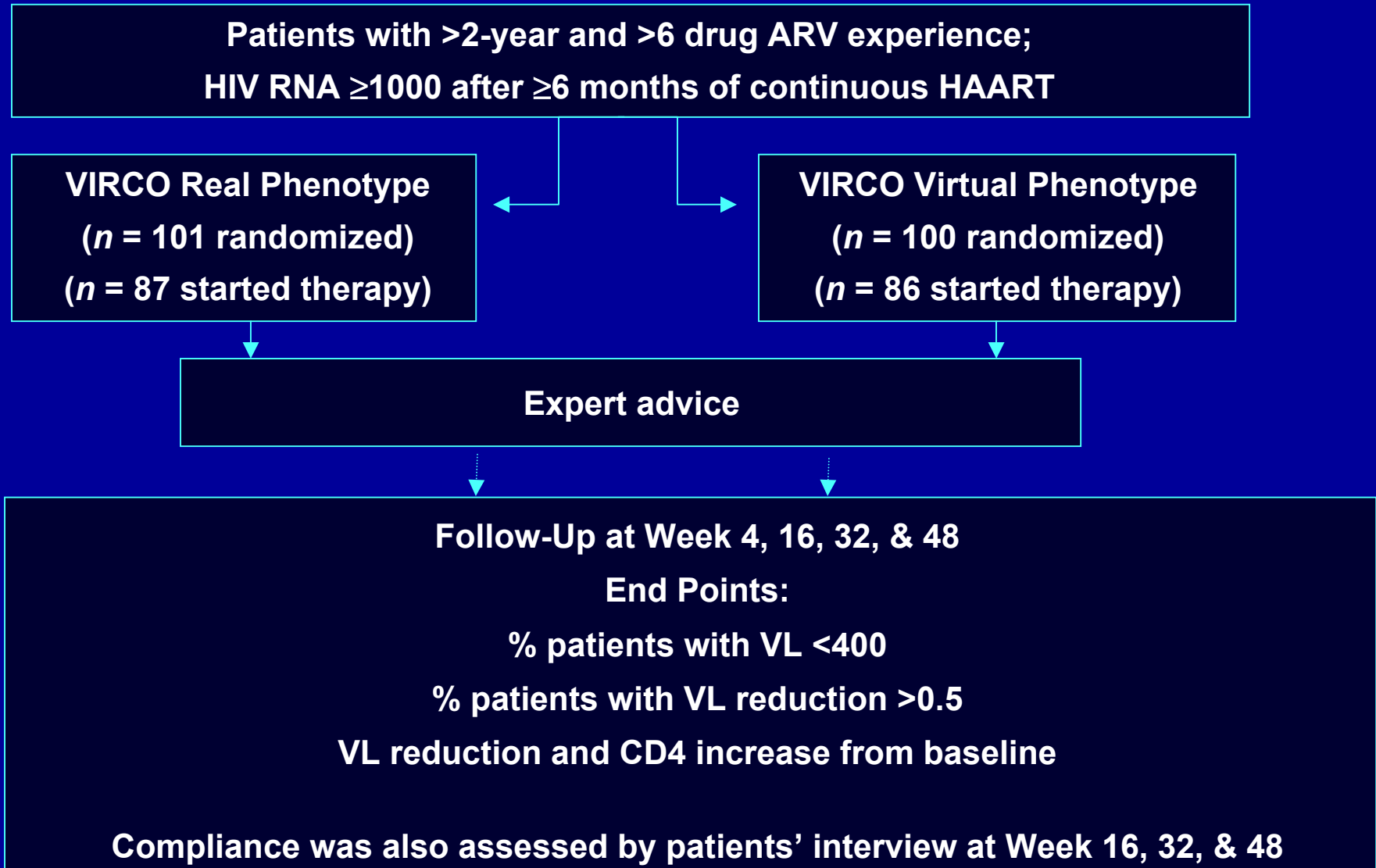
Objectives

- ✓ **To compare viro-immunological outcome after therapy has been changed on the basis of real-phenotype (r-PHT) vs. v-PHT results, both with expert advice, in a population of heavily pre-treated patients**
- ✓ **Moreover, we have investigated the influence of other factors which impact on the clinical response to orientate the best usage of such testing in clinical practice**

Genpherex: Real vs Virtual Phenotype in Experienced Patients

- ✓ Multicenter randomized study set up in 1999 nested within the Italian HIV Ma.S.Te.R. Cohort
- ✓ Compare viro-immunological response to salvage therapy selected after real (Antivirogram[®]) vs virtual phenotype (*VirtualPhenotype*[™]) in heavily pretreated patients failing HAART
- ✓ Resistance testing was performed at Virco, results were interpreted with the 4-10 laboratory available cutoffs

Flowchart of the Study Interventions



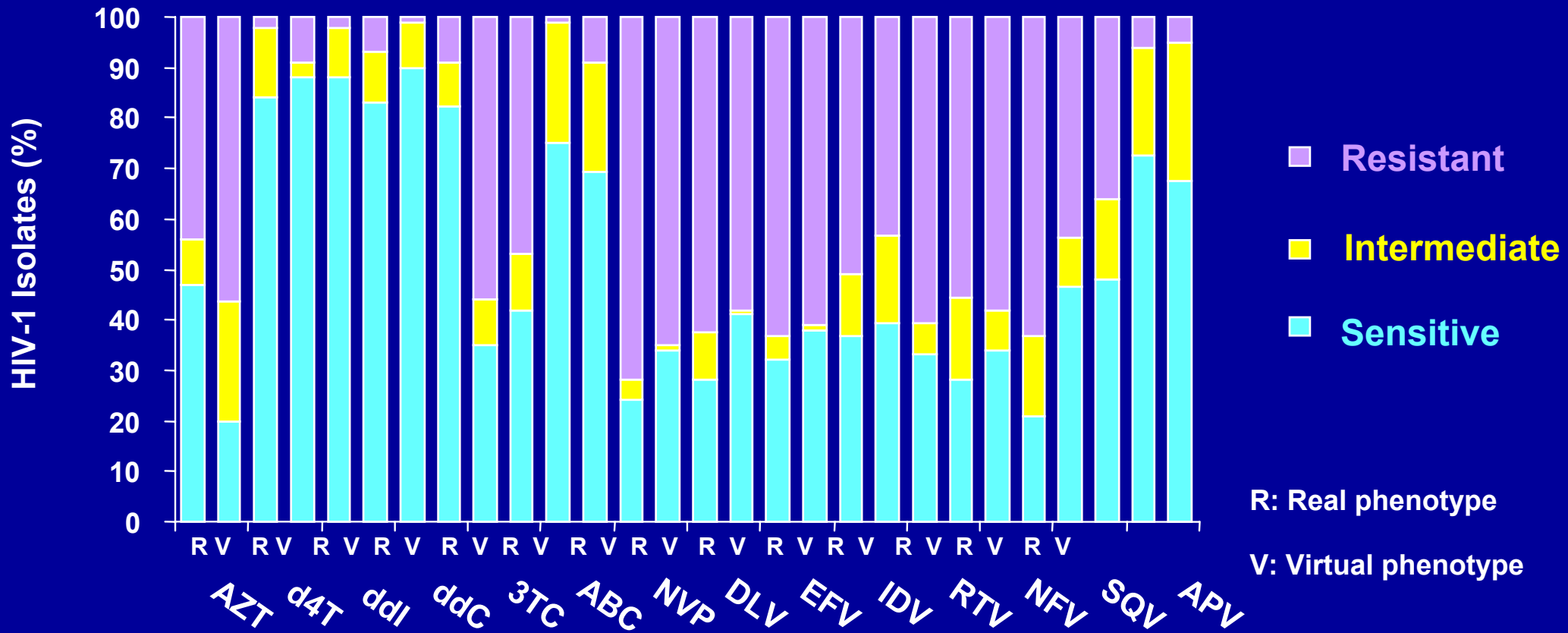
Baseline Characteristics

	Real Phenotype (<i>n</i> = 87)	Virtual Phenotype (<i>n</i> = 86)
Age (years)	38.8 ± 6.04	39.82 ± 7.49
Gender (%)	68 (75.9%)	70 (79.5%)
Mean plasma viral load	4.92 ± 0.623	4.73 ± 0.61
Mean CD4 cell count	248.2 ± 192.7	262.58 ± 238.8
Number of experienced NRTIs	4.71 ± 0.94	4.53 ± 0.59
Duration (months)	57.90 ± 20.95	61.73 ± 24.48
Number of experienced NNRTIs	1.13 ± 0.59	0.92 ± 0.66
Duration (months)	9.16 ± 8.20	9.77 ± 8.29
Number of experienced PIs	3.24 ± 0.83	3.08 ± 0.94
Duration (months)	32.68 ± 10. 48	32.73 ± 12.36

GenPherex: Technical Cutoffs

Real and Virtual

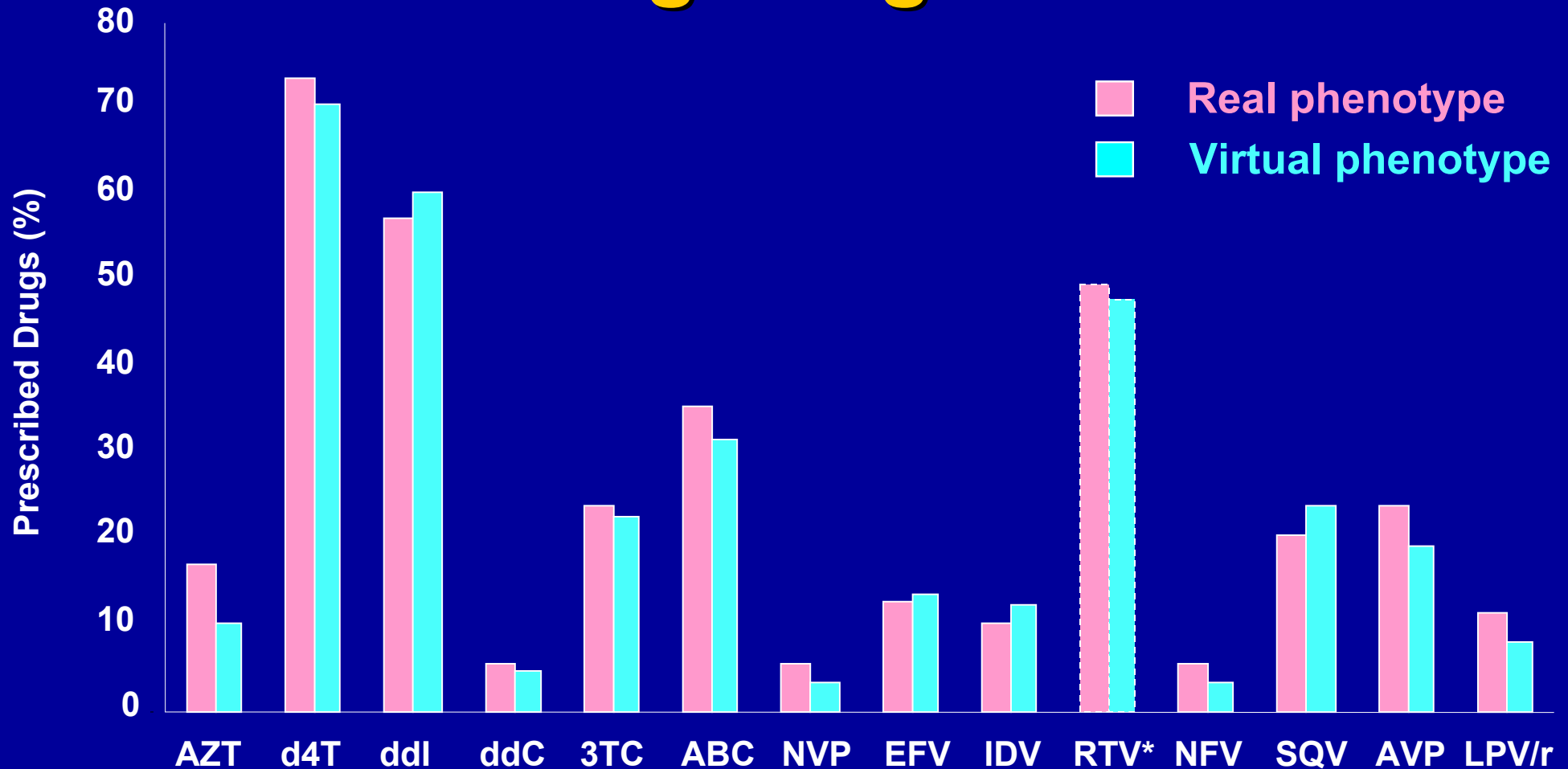
Phenotypic Resistance at Baseline



Characteristics of the Prescribed Regimens

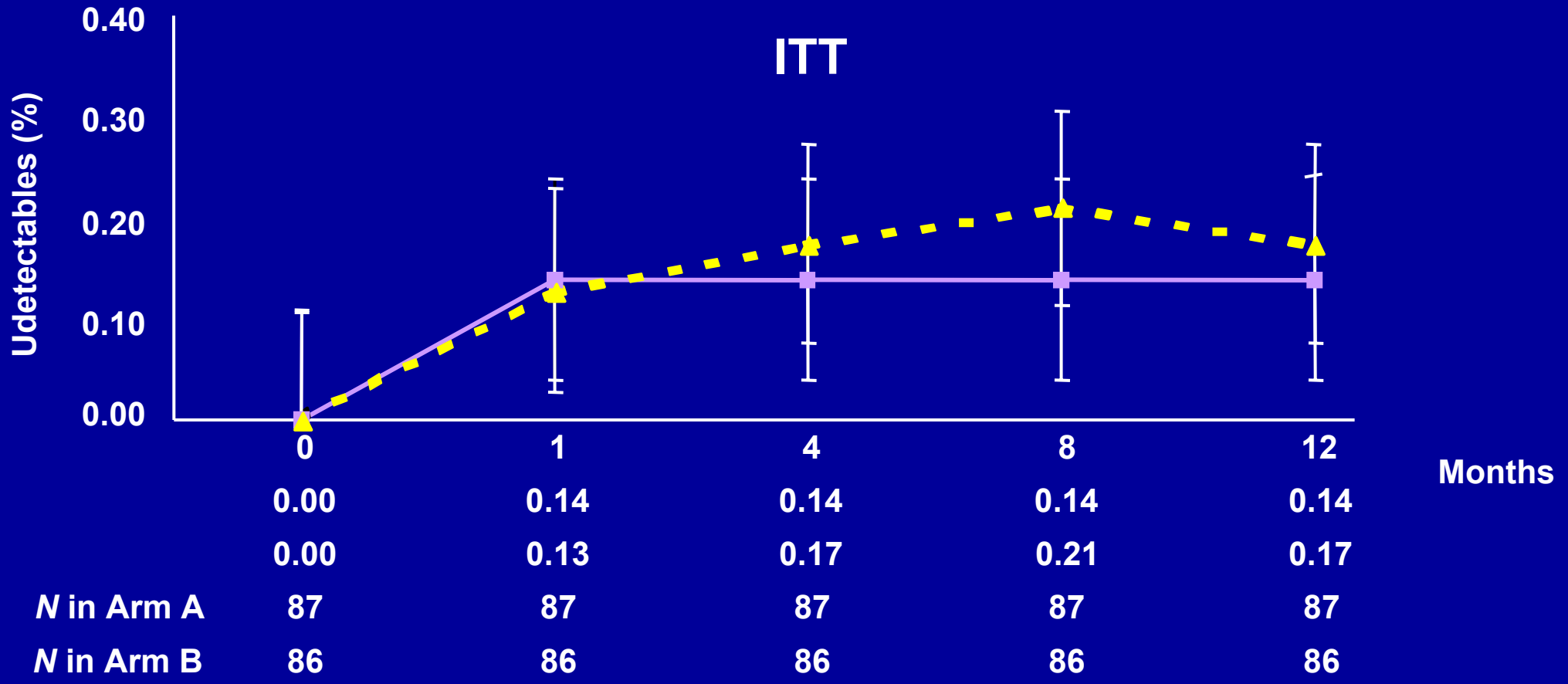
	Real Phenotype (<i>n</i> = 87)	Virtual Phenotype (<i>n</i> = 86)
Number of drugs	3.05 ± 0.26	2.84 ± 0.77
NNRTI-containing (%)	10/87 (11.5)	10/86 (11.6)
PI-containing (%)	56/87 (64.4)	49/86 (57.0)
RTV-boosted (%)	43/56 (76.8)	43/49 (87.7)
NRTI + NNRTI + PI (%)	6/87 (6.9)	8/86 (9.3)
Others (%)	15/87 (17.2)	19/86 (18.6)
Adherence to the expert recommendations	75%	74%

Drugs Used for the Salvage Regimens

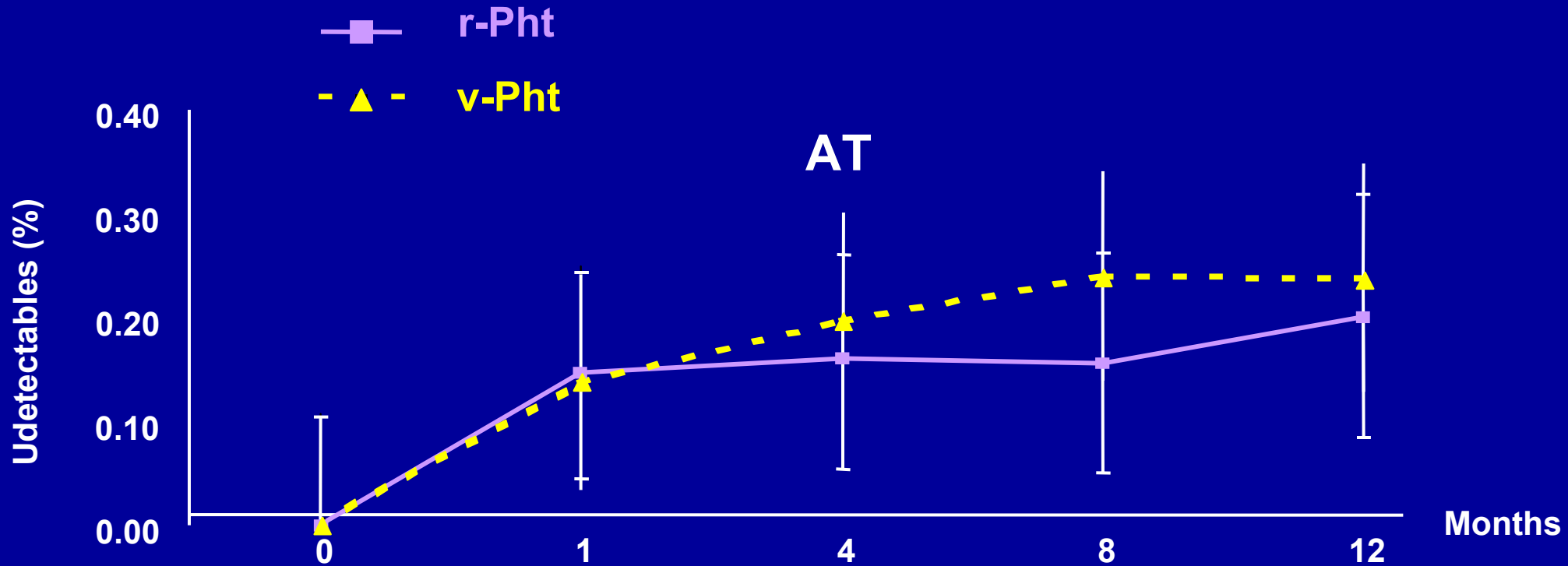


* RTV was always prescribed as baby-dose

Proportions of Undetectable HIV RNA <400

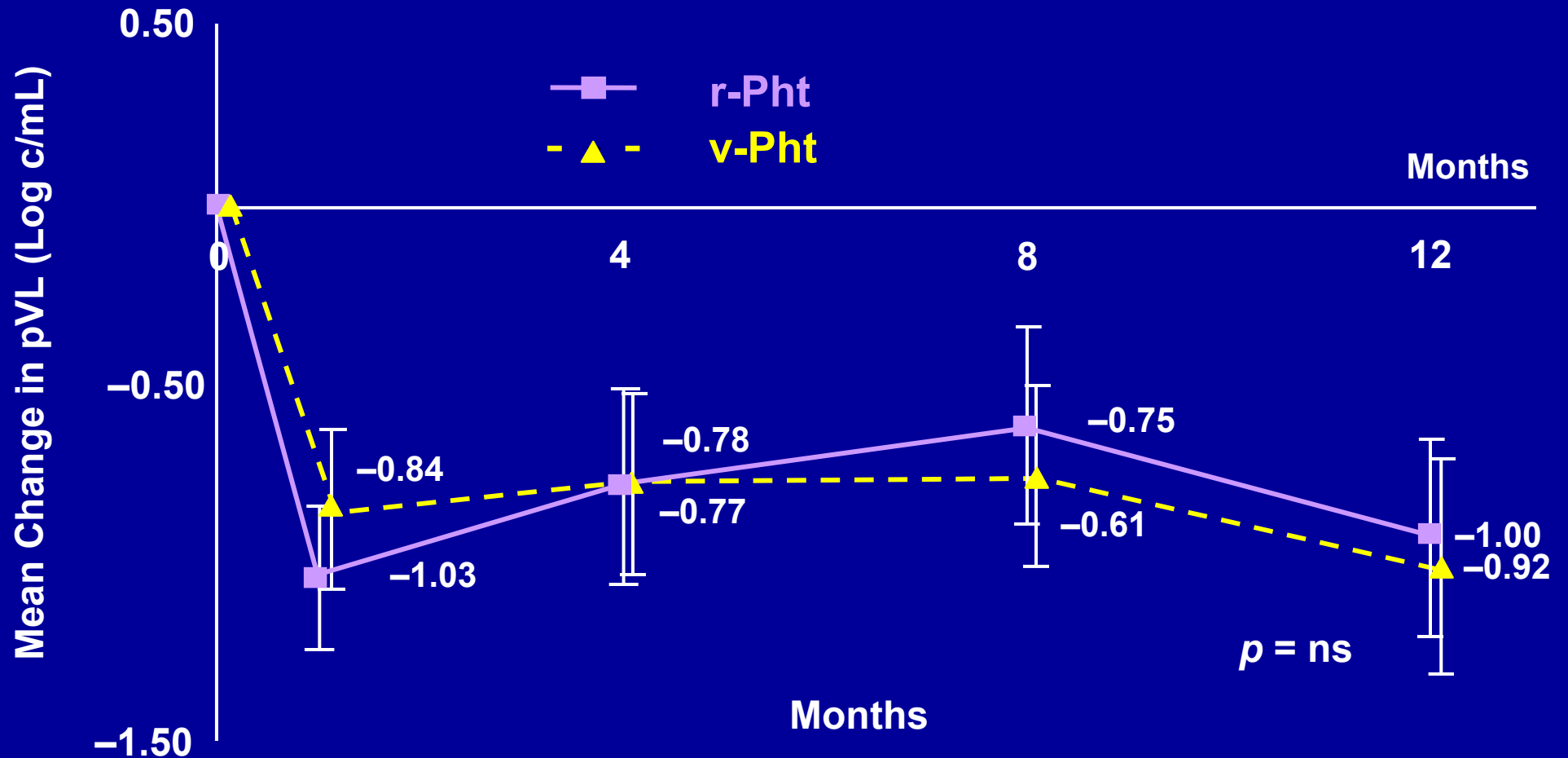


Proportions of Undetectable HIV RNA <400

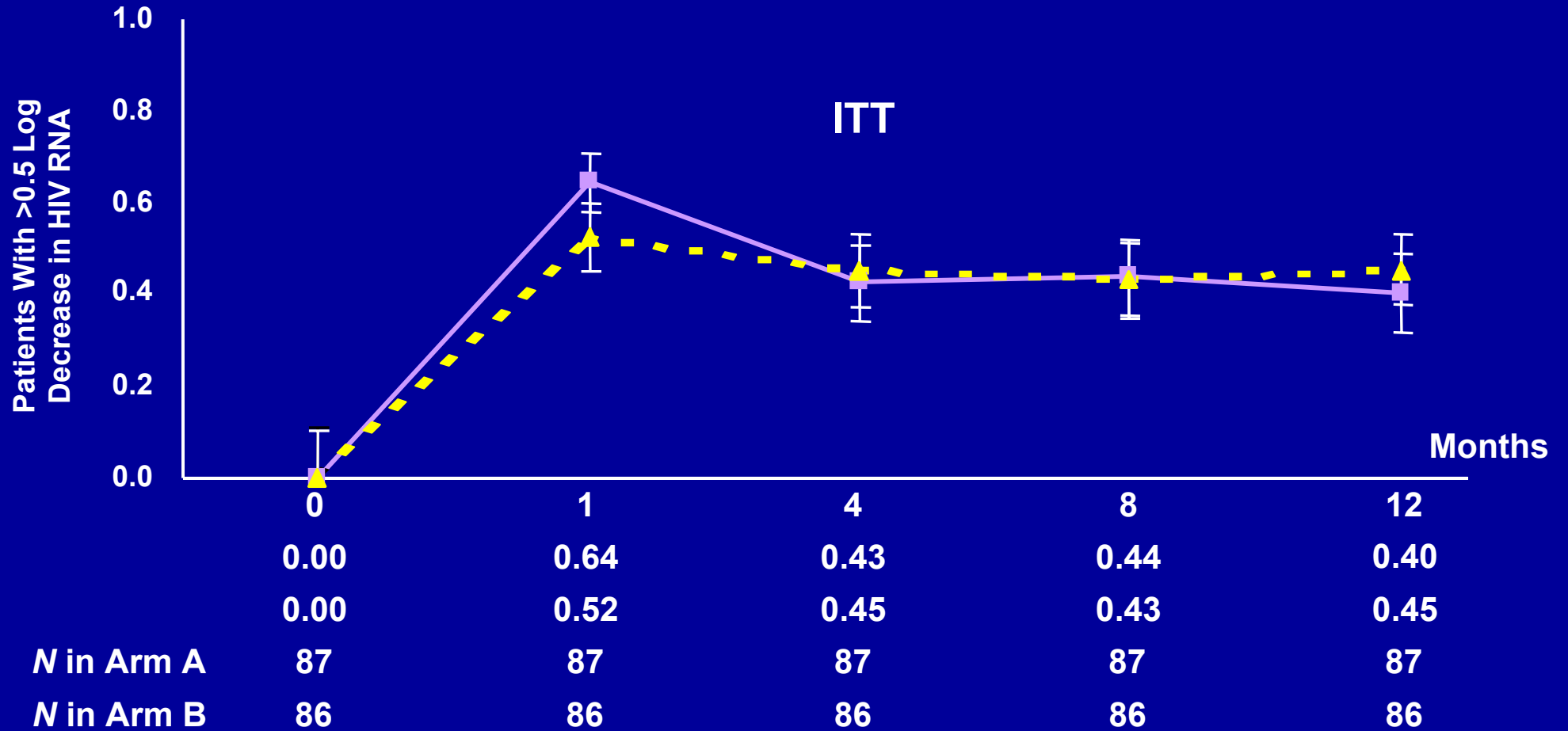


	0	1	4	8	12
	0.00	0.15	0.16	0.16	0.20
	0.00	0.14	0.20	0.24	0.24
<i>N</i> in Arm A	87	82	75	77	60
<i>N</i> in Arm B	86	80	76	75	63

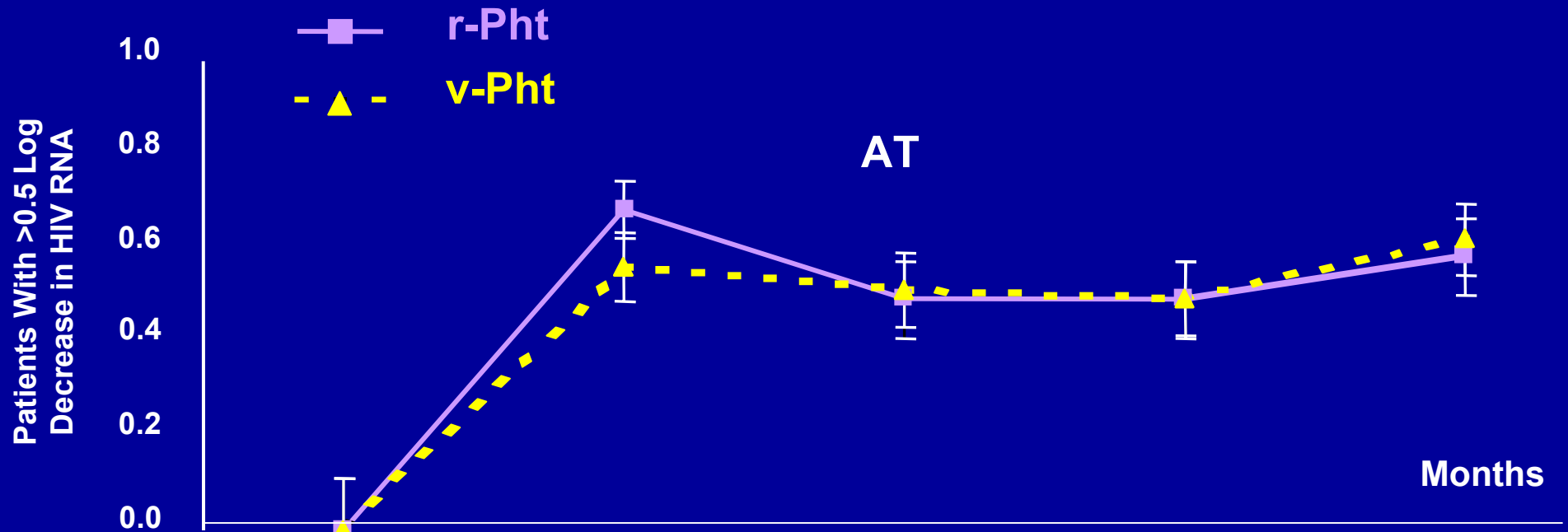
HIV RNA Reduction



HIV RNA Reduction By >0.5 Log copies/mL

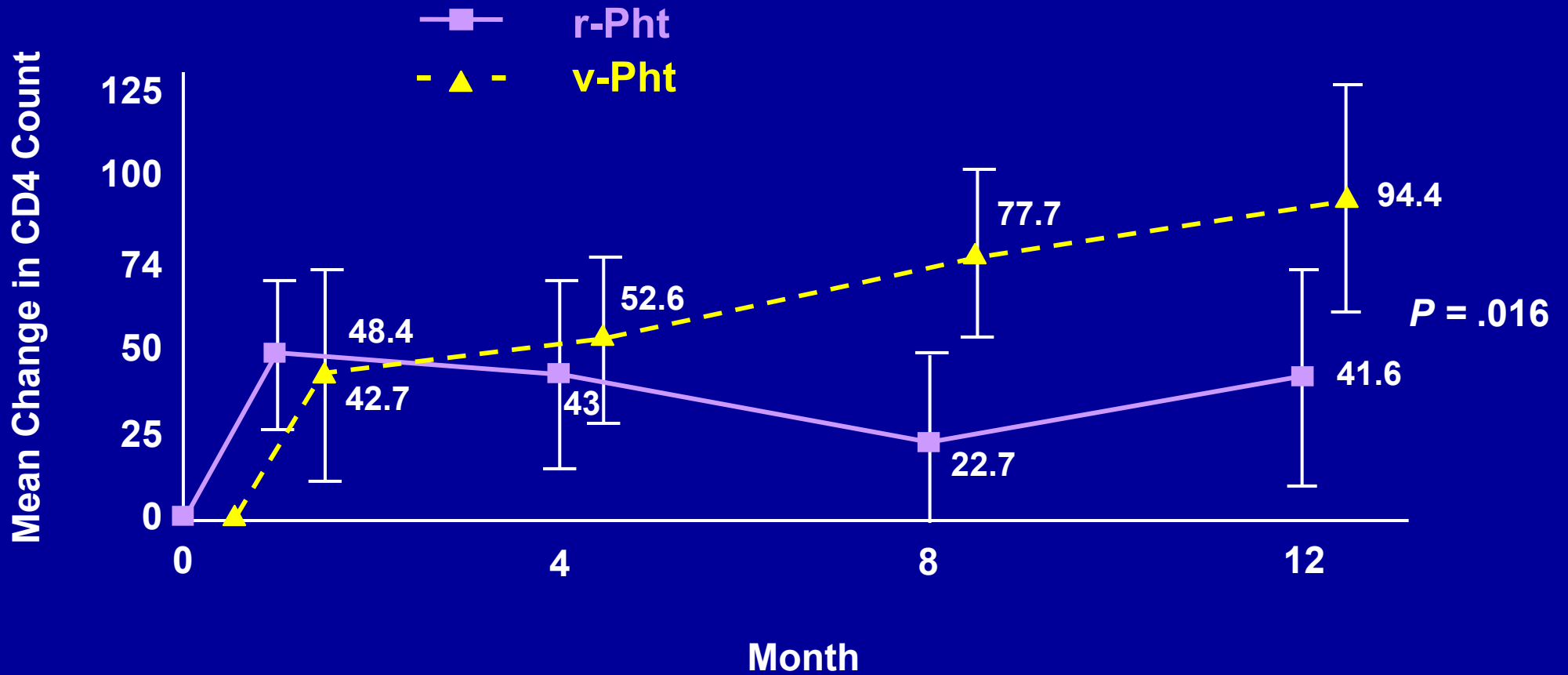


HIV RNA Reduction By >0.5 Log copies/mL



	0	1	4	8	12
	0.00	0.68	0.49	0.49	0.58
	0.00	0.56	0.51	0.49	0.62
N in Arm A	87	82	75	77	60
N in Arm B	86	80	76	75	63

CD4 Cell Increase

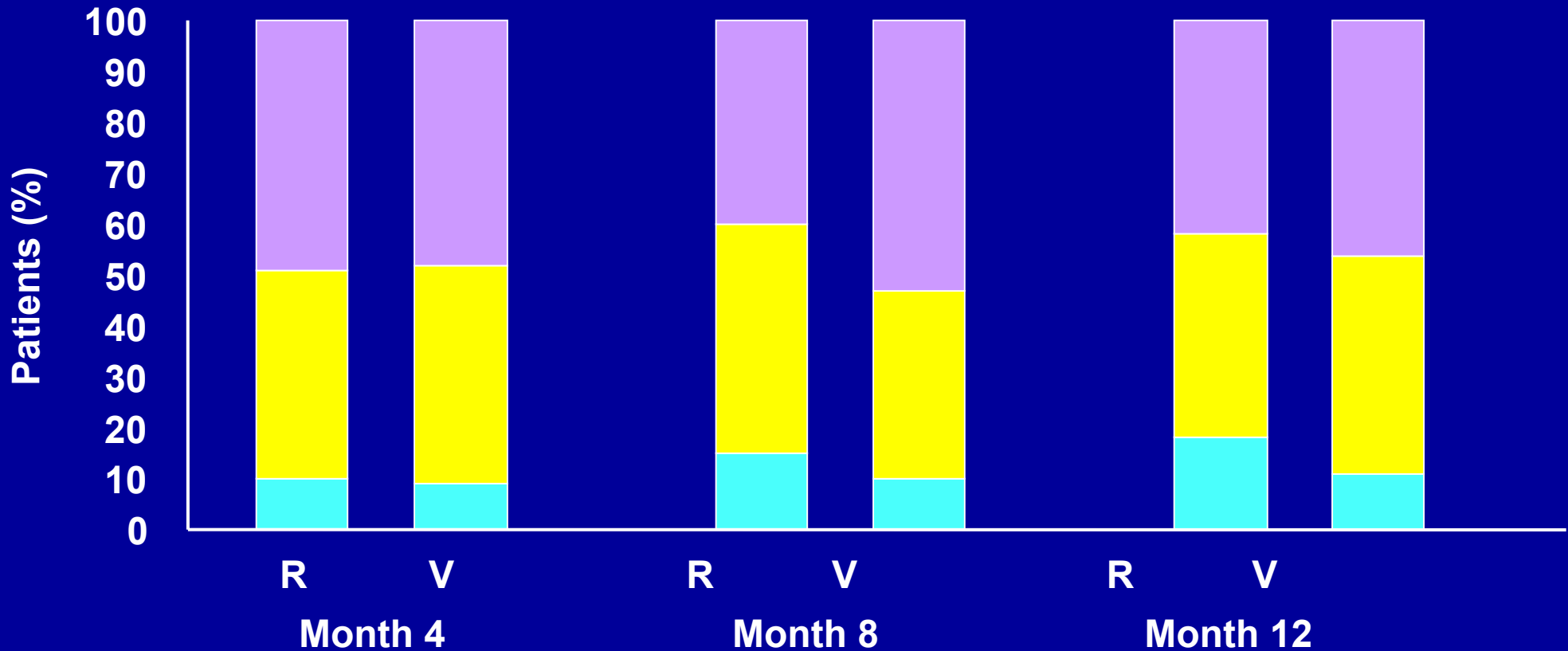


Adherence to Antiretroviral Therapy: Patients' Interviews

■ Scarce (<50% doses last week)

■ Fair (50%-80%)

■ Good (>80%)



R = Real phenotype V = Virtual phenotype

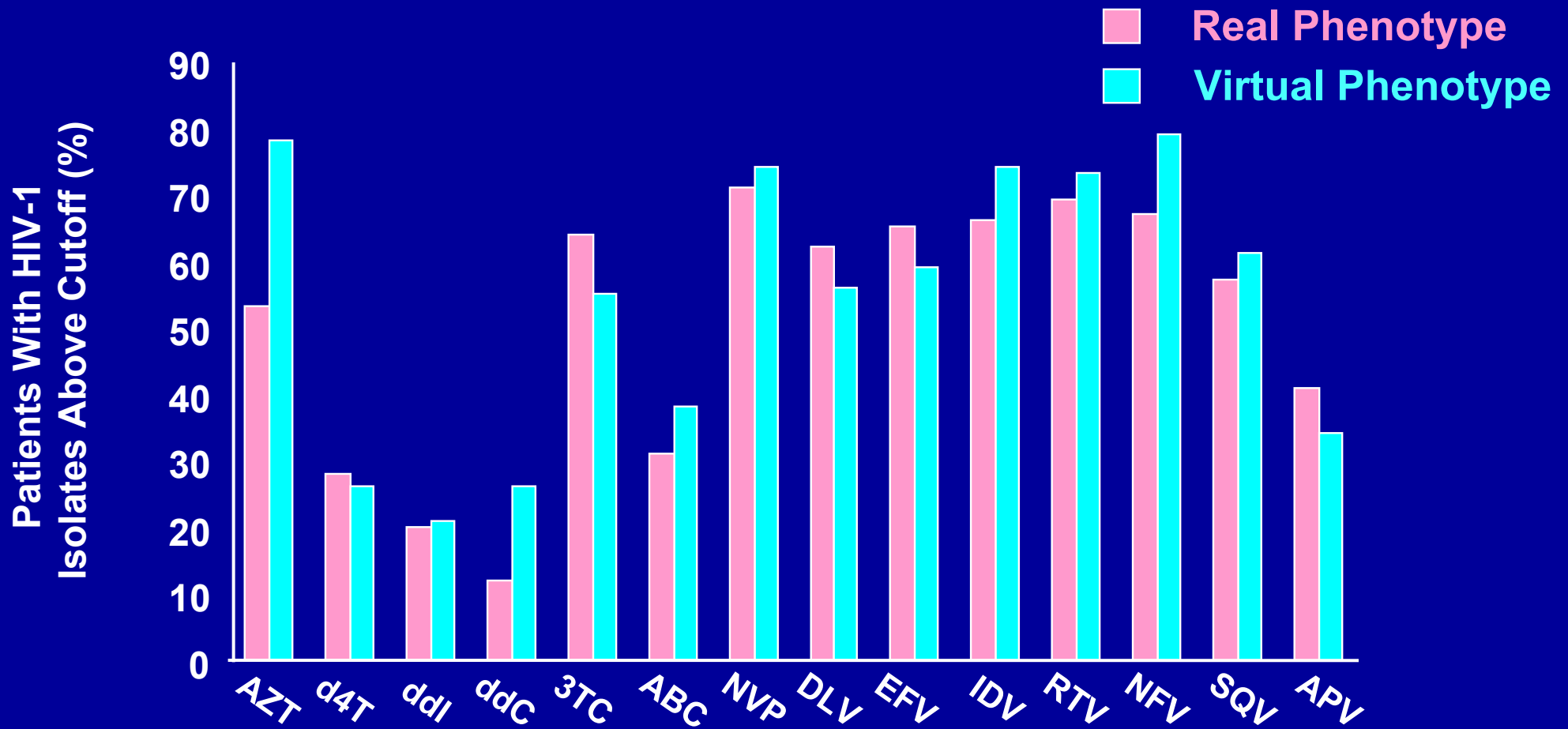
Conclusions

- ✓ **Prevalence of resistance of HIV isolates were comparable in both arms**
- ✓ **Drug prescription reflected low prevalence of drug resistance for certain drugs (D4T > DDI > ABC)**
- ✓ **Virological outcome did not differ when Real or Virtual Phenotype was used in this cohort of highly experienced patients**
- ✓ **Significant reductions in viral load achieved despite low rate of undetectability**
- ✓ **CD4 cell count improved in both arms with a trend for a better immunological response in the Virtual Phenotype arm**
- ✓ **In conclusion, these results suggest that virtual phenotype is as reliable as the standard phenotypic assay in current clinical practice**

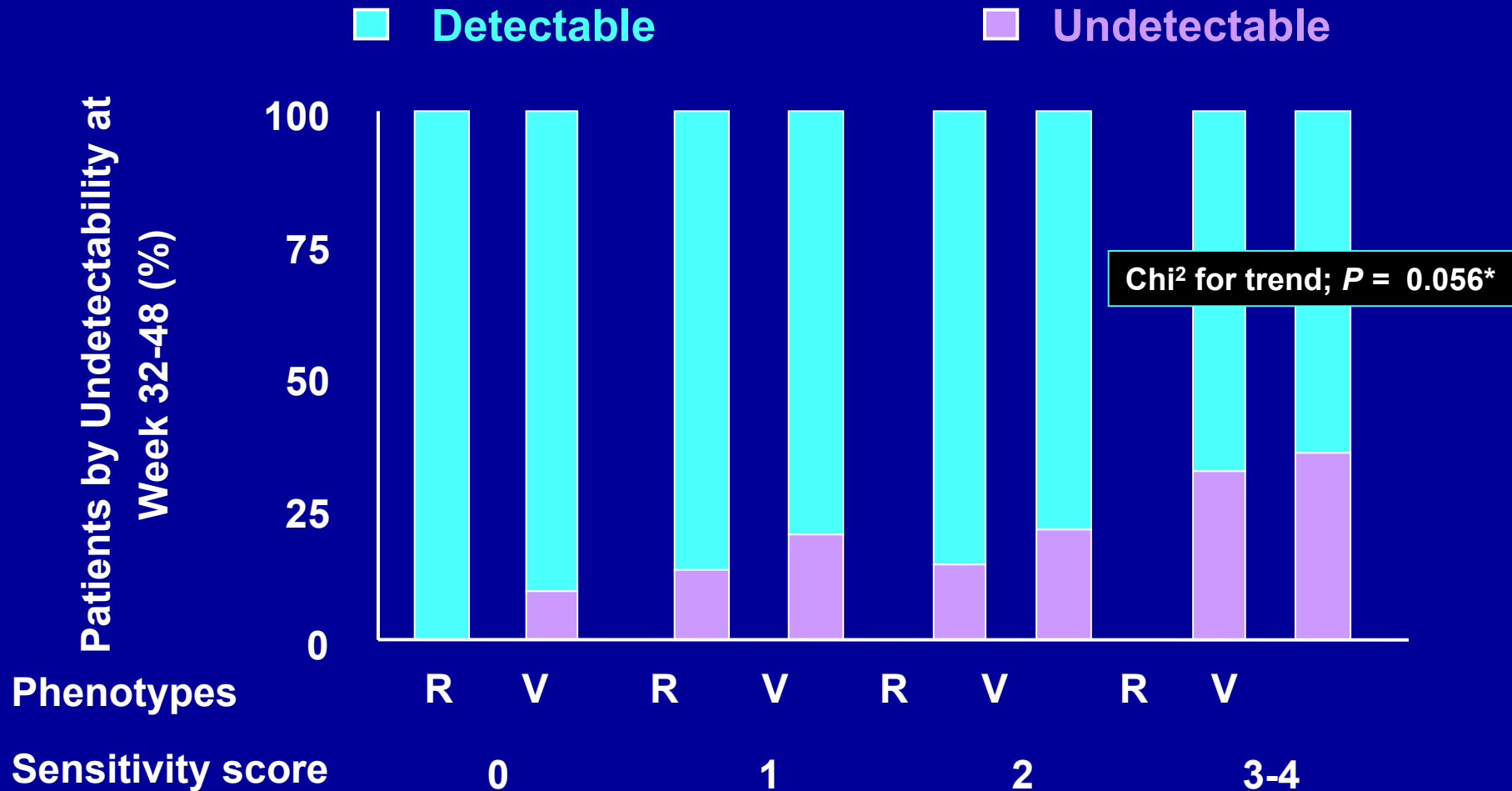
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Biological Cutoffs Real and Virtual Phenotypic Resistance at Baseline



Sensitivity Score vs Virological Response



R = Real phenotype V = Virtual phenotype

Sensitivity score is the number of drugs in the prescribed regimens that resulted sensitive as by the new biological cut-offs (except for ritonavir which was always used at baby-dose)

* P value reported for all patients (R = Real phenotype + V = Virtual phenotype)

Predictors of Virological Outcome

Multivariate Models

Covariates	O.R.	95% C.I.	<i>P</i>
Arms	0.78	0.33-1.84	0.568
BL CD4/mm ³	3.39	1.26-9.12	0.016
BL Log ₁₀ HIV-RNA	1.85	0.73- 4.69	0.197
Adherence W32	0.31	0.14-0.67	0.003
Sensitivity			
Score *	1.99	1.17-3.37	0.011
Arms	0.81	0.34-1.94	0.633
BL CD4/mm ³	4.19	1.51-11.67	0.006
BL Log ₁₀ HIV-RNA	1.70	0.66- 4.34	0.268
Adherence W32	0.31	0.14-0.67	0.003
Number of new and sensitive drugs *	2.64	1.38-5.02	0.003

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

Conclusions II

- ✓ **Resistance pattern did not differ significantly when the new “biological” cut-offs were applied**
- ✓ **Multivariate analyses showed resistance, adherence and baseline CD4 to be correlated with the virological outcome**
- ✓ **The introduction of sensitive drugs never used by patients correlated with better virological outcome**
- ✓ **These results suggest that benefit of resistance testing may be improved, providing that other factors (resistance, adherence, CD4 and treatment history) are considered in the clinical practice**