What are the scientific and clinical questions for which sophisticated quantitative methods are needed?

Françoise Brun-Vézinet

MD, PhD

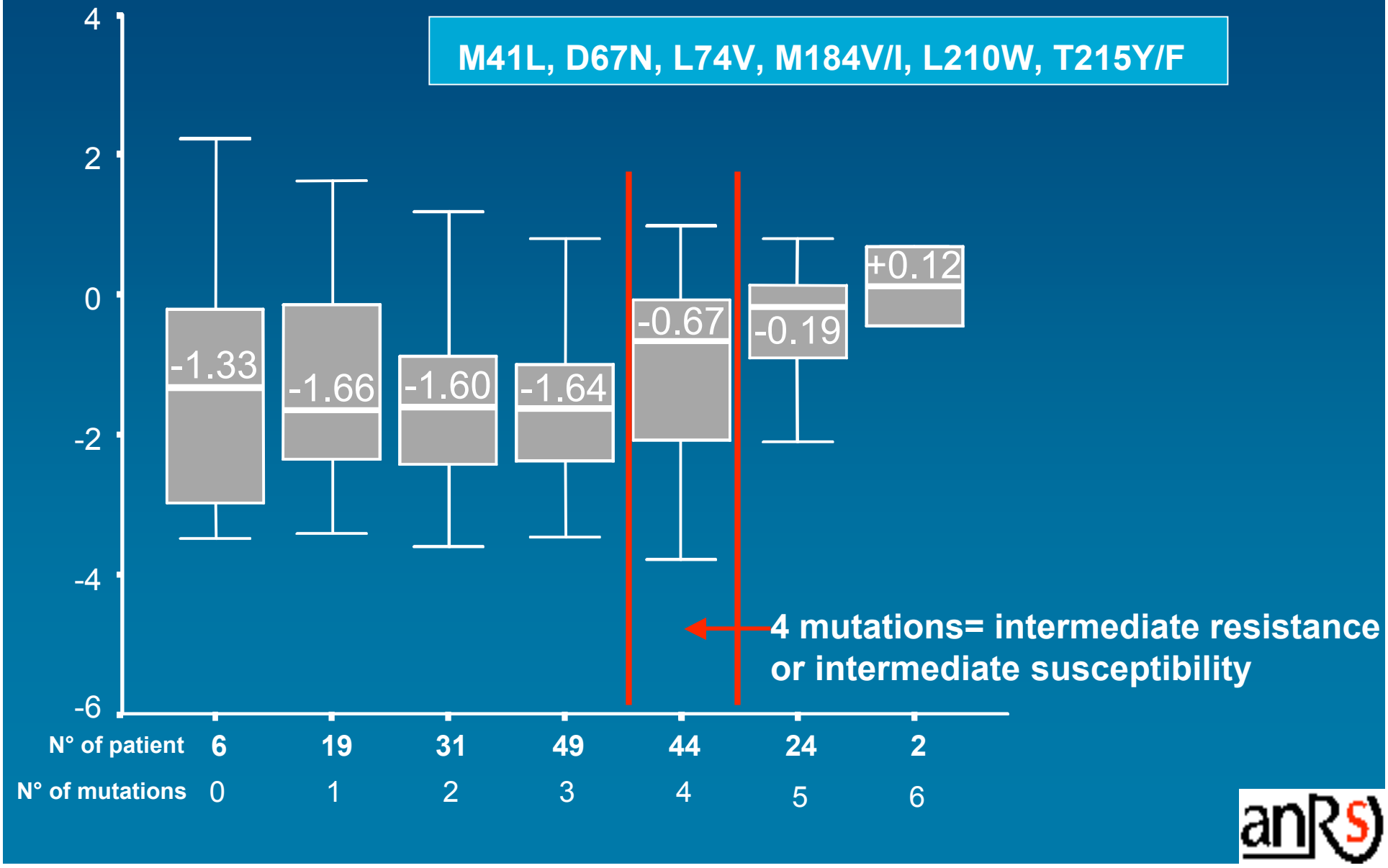
Medical Virologist: Some Questions

- Genotype:
  - Defining categories: resistant, **potentially resistant?**, no evidence of resistance
  - How to weight resistance mutations? mixtures WT/M?
- Define data source to use for algorithms:
  - W4, W8, W24?
  - Which HIV RNA measure?
  - AT? ITT?
  - Clinical trial, cohorts

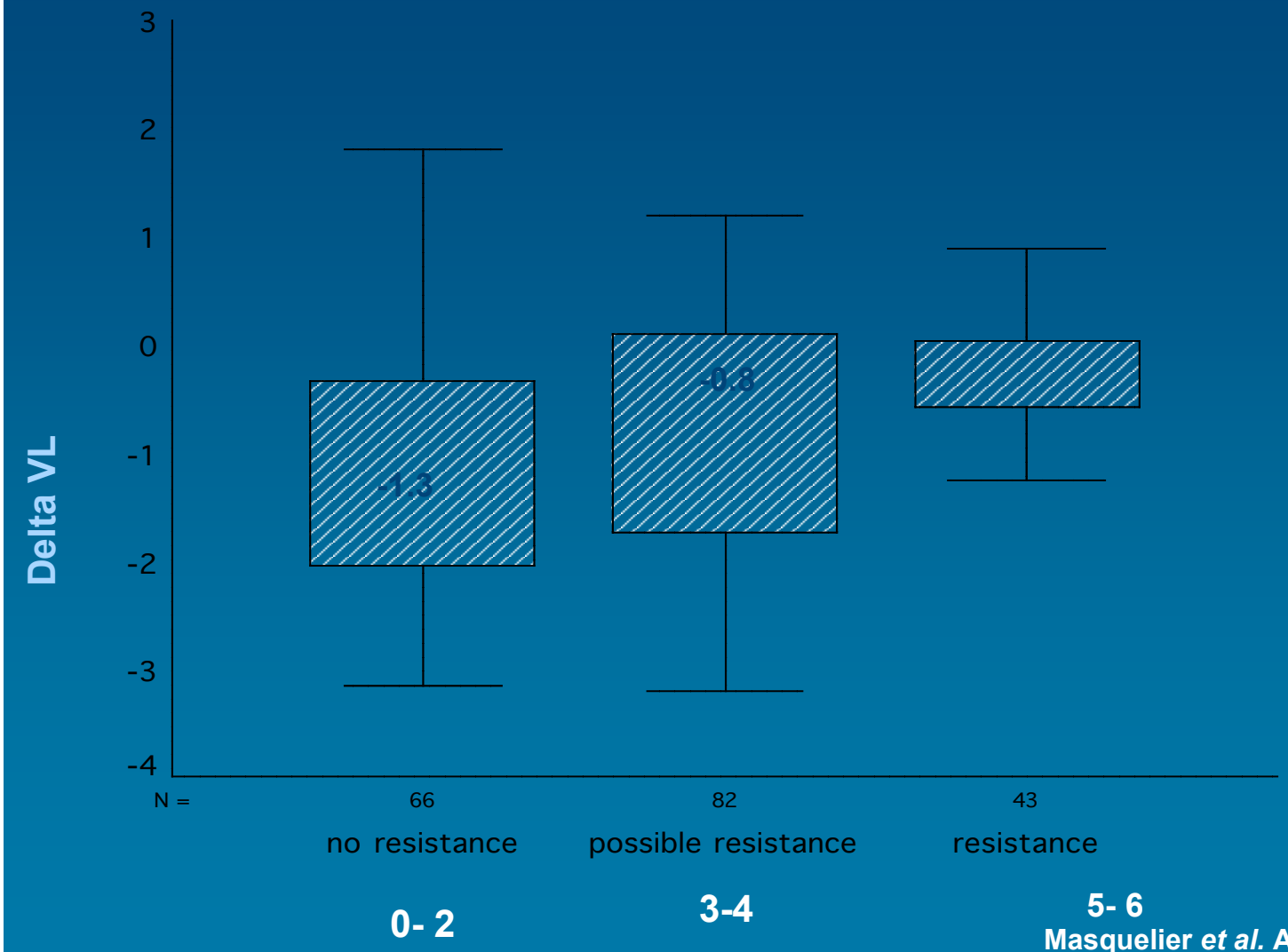
Genotype: definition of « potentially » susceptible? or « potentially » resistant?

- Is it needed to be standardized?
- Is it possible to be standardized?
  - A priori: resistance is a continuum….
- Are the same set of mutations involved in resistance and potential resistance?

Clinically relevant interpretation of genotype for resistance to abacavir (*AIDS 2003)*



TDF: Mutation score and virological response (M3)



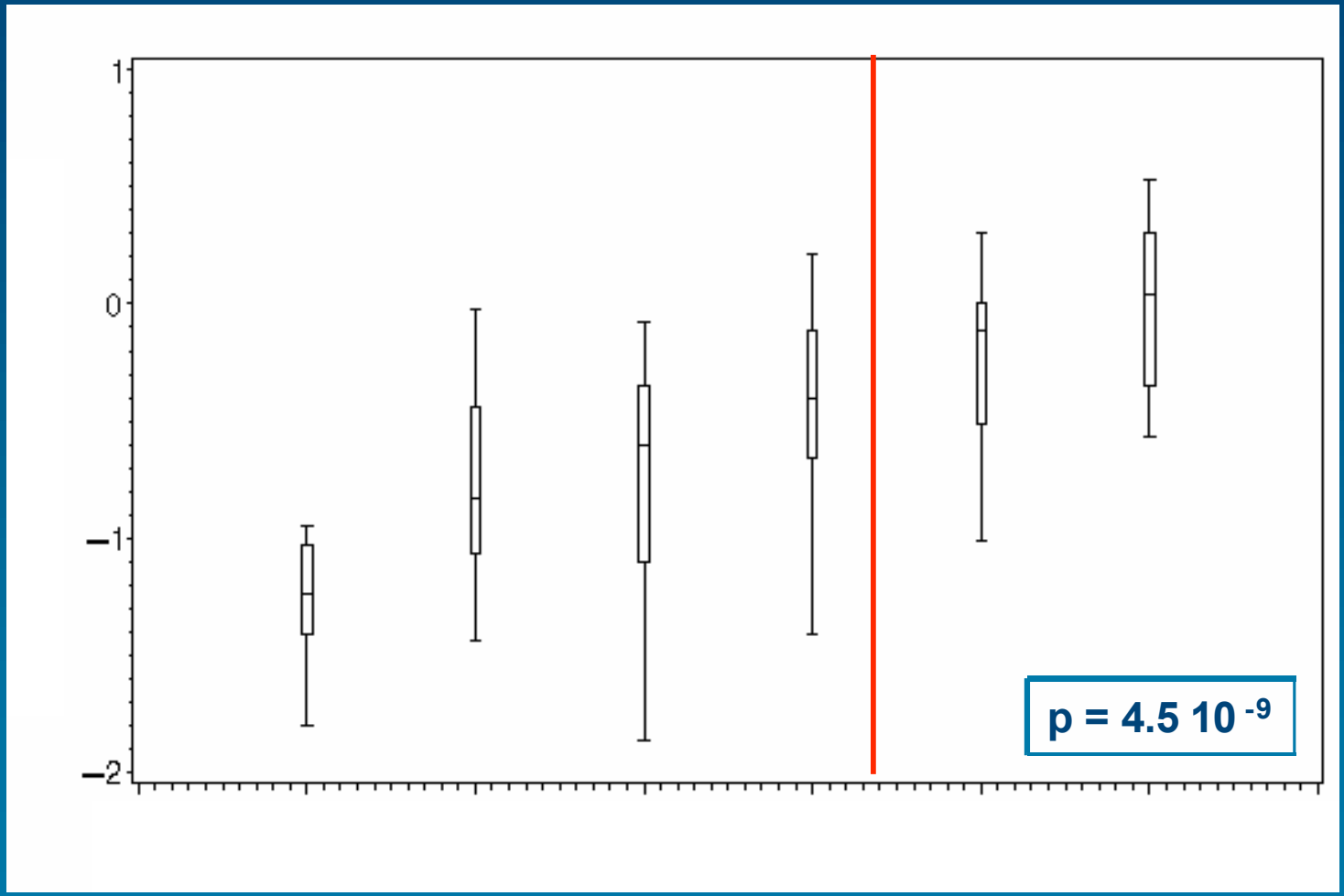
$p < 0.001$

Masquelier *et al.* Antivir Ther 2004; 9:315-323

Mutation score: number of mutations among 41L+67N+210W+215Y/F + 69D/N/S + 44D

Median decrease in HIV-1 plasma RNA at week 4 according to the genotypic score computed as M41L – M184V/I + L74V + T69D + T215Y/F – K70R + K219Q/E

ddl (Jaguar)



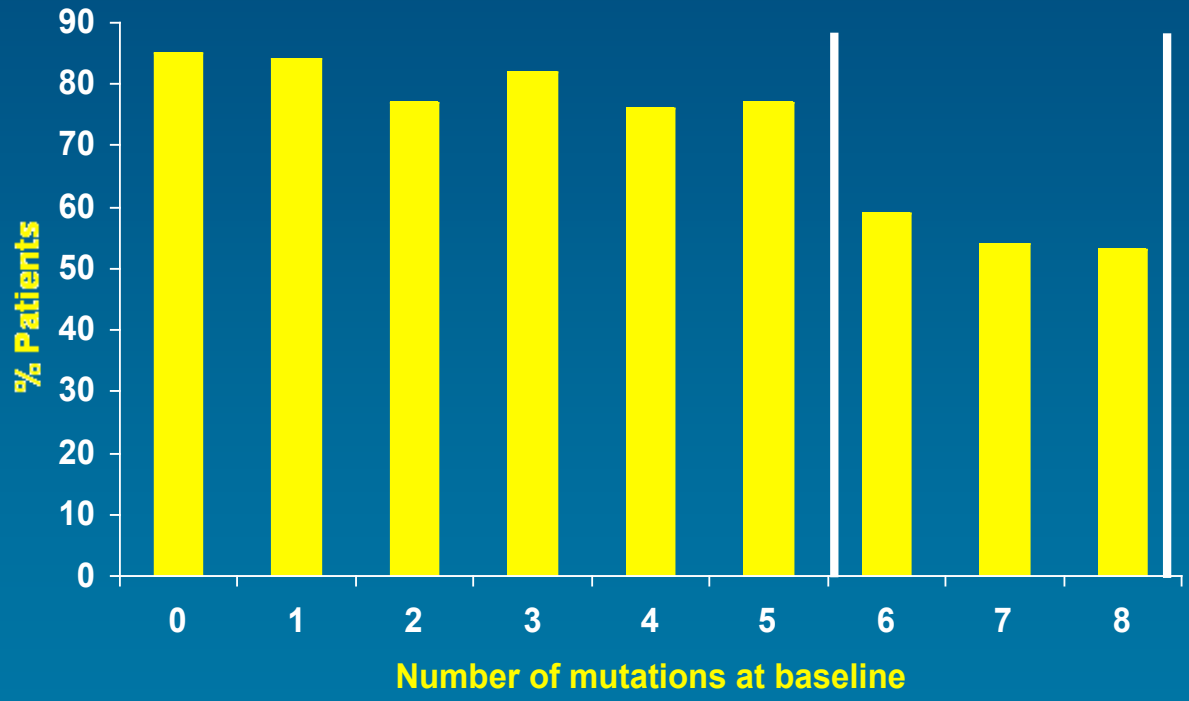
Genotypic score	-2	-1	0	1	2	3
Patients (n)	8	30	16	30	12	6

LPV (ATU): Baseline Characteristics (700 patients)

Gender	
Male	82.5%
Age (years)	
Mean	41
Median	40
CDC Classification (N = 675)	
Asymptomatic (Stade A)	14.7%
Symptomatic (Stade B)	31.3%
AIDS – Indicator (Stade C)	54.1%
HIV diagnosis date (N = 610)	
< 1990	41.6%
1990 – 1995	42.3%
≥ 1995	16.1%
Prior ARV use (median)	
PIs	**3**
NRTIs	**5**
NNRTIs	**1**

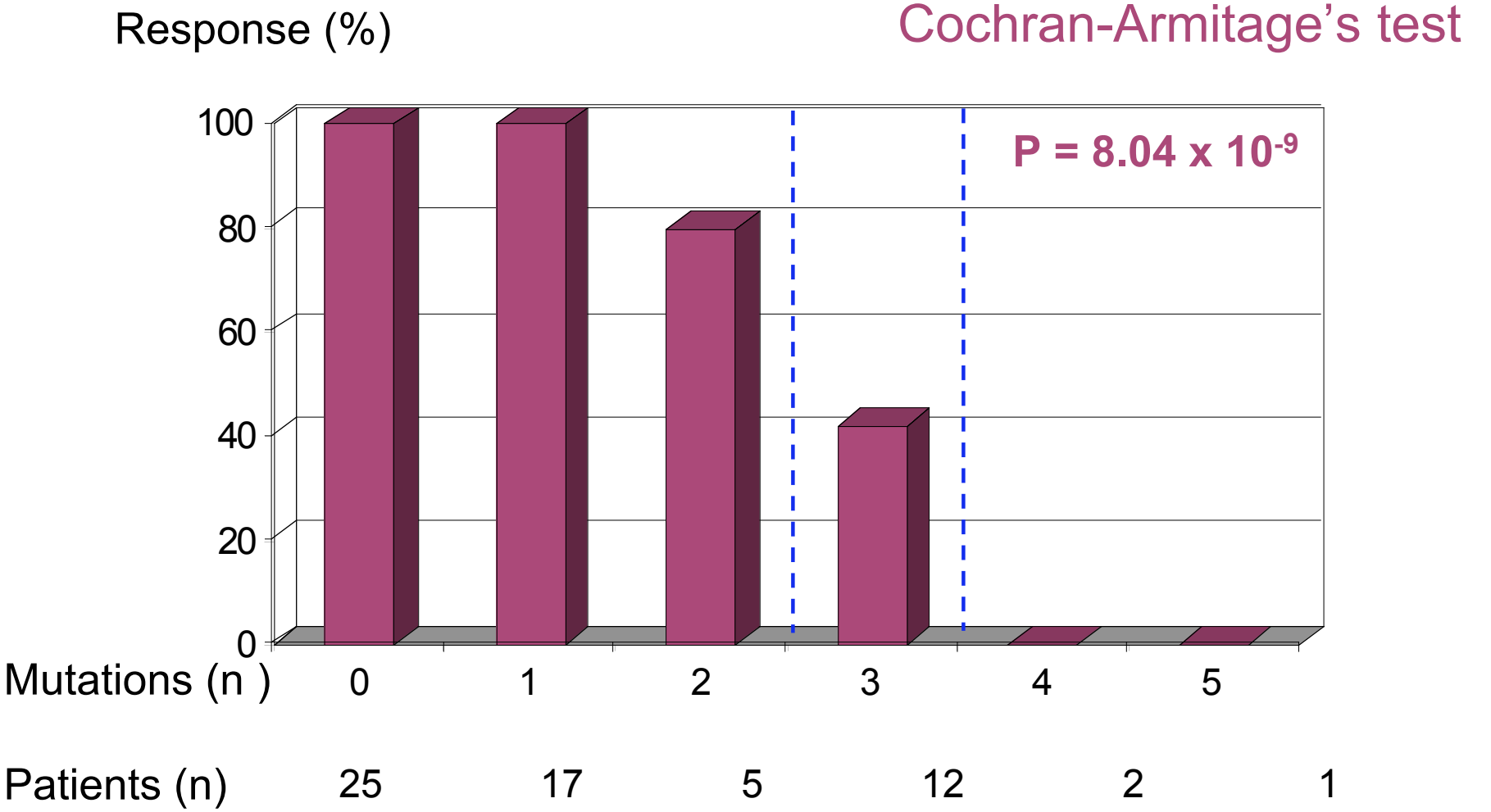
CD_4 count (cells/mm^3)	
< 50	23.1%
50 – 150	28.3%
≥ 150	48.6%
Mean	177
Median	**144**
Standard Deviation	160
Minimum	0
Maximum	995
HIV RNA (Log_{10} copies/mL)	
< 5 Log_{10} copies/mL	56.6%
≥ 5 Log_{10} copies/mL	43.4%
Mean	4.83
Median	**4.88**
Standard Deviation	0.76
Minimum	1.54
Maximum	6.98

Virologic response: VL <400 copies/mL and/or a 1 log decrease with respect to baseline number of LPV mutations at 11 codons L10FIRV, K20MR, L24I, M46IL, F53L, I54LTV, L63P, A71ITV, V82AFT, I84V, L90M



- LPV mutation score of 5 or less: virologic response fairly uniform
- LPV mutation score of 6 or more: Lower response
- Genotypic breakpoint for LPV/r using the LPV mutation score : between 5 and 6 mutations

ATV/RTV Resistance Score: at M3: > ↘ 1 log HIV RNA) (10, 16, 33, 46, 60, 84, 85)



all bootstrap samples, $P < 0.0001$

What is « potential resistance or potential susceptibility? » How to standardize?

- ABC and TDF: median VL response: half of the best median response (-0.7 log)
- ddI: continuum and no clear intermediate response
- LPV: 50% of the patients responded
- ATV/r: between 40% and 80% of patients responded
- What is the best definition of potential susceptibility???

HIVdb: 5 categories with scoring of mutations

- Susceptible: 0-9
- Potential low resistance: 10-14 (mut which by themselves may not cause drug resistance)
- Low level resistance: 15-29 (suboptimal virologic response)
- Intermediate resistance: 30-59 (between low and high)
- High level resistance: =>60

GSS

- **The most frequent questions: « according to the genotypic results of this patient, is it still possible with a combination of drugs**
  - to decrease VL of 1log, 1.5 log…..?
  - To achieve less than 200c/ml, 50c/ml?
- **GSS: sum of active drugs**
  - 1 for each drug without evidence of resistance, 0.5 for… and 0 for…..????
  - How to conciliate the GSS and the most frequent questions?

How to weight resistance mutations in algorithms?

Mutations associated with positive impact on viral load decrease Jaguar trial: *Univariate analysis in ddI arm (p<0.20)*

AG Marcelin, AAC 2005

		ddI	
		n	median RNA change
M184V			
	Absent	**8**	**- 0.15**
	Present	**93**	**- 0.60**
K70R			
	Absent	**74**	**- 0.44**
	Present	**27**	**- 0.94**

ddI??

ANRS

- 41L: +1
- 74V: +1
- 215Y/F: +1
- 219E/Q: +1
- 210W: +1
- 69D: +1

- 184V: -1
- 70R: -1

HIVdb

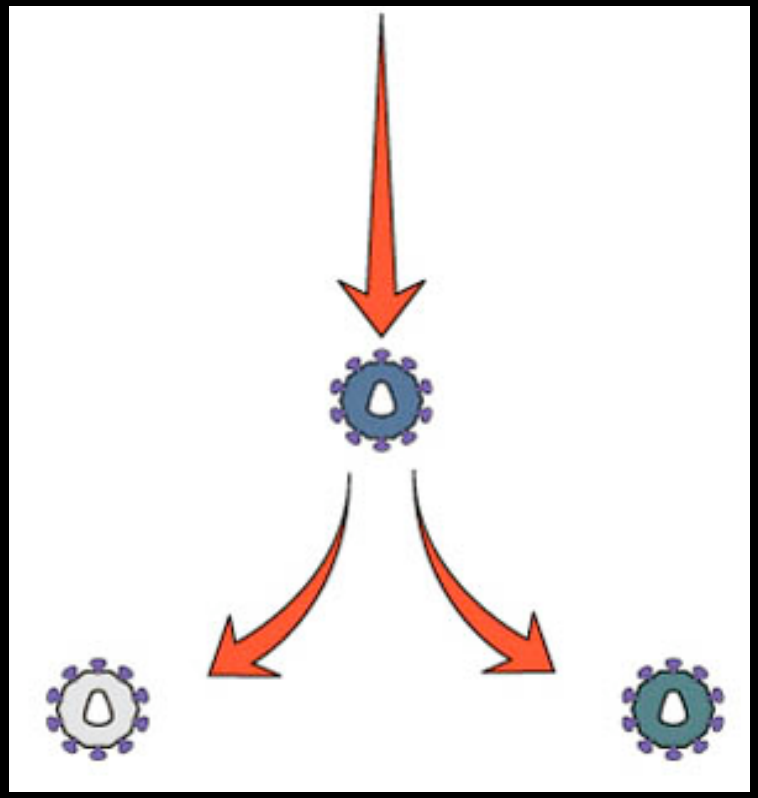
- 41L: 12
- 74V: 55
- 215Y/F: 20/20
- 219E/Q: 0/0
- 210W: 12
- 69D: 25

- 184V: +5
- 70R: 0

How to weight the mutations? Which criteria? Which methods?

Dichotomous Pathways to Resistance

AZT or d4T



Unknown factors

41L
210W
215Y

Higher level AZT resistance
More NRTI cross-resistance
Less decrease in resistance with M184V

Unknown factors

215F
70R
219Q
67N???

Lower level AZT resistance
Less NRTI cross-resistance
Greater decrease in resistance with M184V

Questions:

- Is there also an impact of TAMs pattern 2 on the activity of other nucleoside analogs besides TDF?
- ANRS scores
  - ABC: no 70, no 219, +67
  - TDF: no 70, no 219, +67
  - ddI: no 70, no 67, +219
- Differentiate 215Y and 217F with weighting
- 67 and 219 : pattern 1 or 2? How to weight?

Influence of new reverse transcriptase mutations on virologic response to didanosine in the didanosine add on Jaguar study

AG Marcelin[1], P Flandre[2], J Pavie[3], N Schmidely[4], M Wirden[1], MC Bernard[4], JM Molina[3] and V Calvez[1]
1 Pitie-Salpetriere Hospital, Paris, France; 2 INSERM 472, Villejuif, France; 3 Saint Louis Hospital, Paris France and 4 BMS, Rueil, France

OBJECTIVE

- **To investigate the role of other RT mutations than known drug resistance mutations on the virological response to ddI.**

CONCLUSIONS

- **2 RT mutations (211 and 228) have the potential to influence negatively the virologic response to ddI and one RT mutation (214), positively the response to ddI.**
- **Taking account these mutations allowed to improve prediction of the response to ddI, especially in patients previously classified as sensitive or intermediate to ddI.**
- **A mutation score, including these new mutations and mutations previously described, is associated with a continuum of virologic response according to the number of these mutations and increased the predictivity of virologic response to ddI.**

to look at every position of the RT??

Marcelin et al. 2005

Medical Virologist: Some Questions

- Genotype:
  - Defining categories: resistant, **potentially resistant?**, no evidence of resistance
  - How to weight resistance mutations? mixtures WT/M?
- Define data source to use for algorithms:
  - W4, W8, W12, W24?: depends on the databases, not the same conclusions (ex: TPV maximum response at W4/8)
  - Which HIV RNA measure?: the most easily translated in clinical practice
  - AT? ITT?: on treatment
  - Clinical trial, cohorts: whatever

Questions: Conclusions

- To define and standardize « potentially resistant »
- Are the same set of mutations involved in resistance and potential resistance?
  - To define intermediate resistance
  - Then to look at the score of mut responding to this definition
  - To analyze the score of mut corresponding to the absence of response
- GSS and potential resistance?
- To weight resistance mutations and mixtures
  - TAMs patters 1 and 2
- To look at every position of RT
- To look at the gag CS for PIs?

Thank You

	Mutations associated to resistance	Mutations associated to « possible resistance »
ZDV	1.T215Y/F 2.At least 3 mutations among : M41L, D67N, K70R, L210W, T215A/C/D/E/G/H/I/L/N/S/V, K219Q/E [1, 2, 3, 4] 3.Q151M 4.Insertion at codon 69	•T215A/C/D/E/G/H/I/L/N/S/V [1, 2, 3, 4]
3TC/FTC	1.M184V/I 2.Insertion at codon 69	1.K65R [11, 12, 16] 2.Q151M
ddI	1.At least a score of + 2 among: M41L + T69D + L74V + T215Y/F + K219Q/E – K70R – M184 V/I [5, 14, 15, 17, 18] 2.Q151M 3.Insertion at codon 69	1.K65R [11, 12] 2.L74V [19]
d4T	1.V75A/M/S/T 2.T215Y/F [6] 3.At least 3 mutations among : M41L, D67N, K70R, L210W, T215A/C/D/E/G/H/I/L/N/S/V, K219Q/E [4, 7, 14, 15] 4.Q151M 5.Insertion at codon 69	•T215A/C/D/E/G/H/I/L/N/S/V [4, 7]
ABC	•At least 5 mutations among : M41L, D67N, L74V, M184V/I, L210W, T215Y/F [8] •K65R and L74V and Y115F and M184V/I 1.Q151M 2.Insertion at codon 69	•4 mutations among : M41L, D67N, L74V, M184V/I, L210W, T215Y/F [8] •K65R [9, 11, 12]
TDF	•At least 6 mutations among: M41L, E44D, D67N, T69D/N/S, L74V, L210W, T215Y/F [13] •K65R [9, 10, 11, 12] •Insertion at codon 69	•3, 4 or 5 mutations among: M41L, E44D, D67N, T69D/N/S, L74V, L210W, T215Y/F [13]