



Les outils

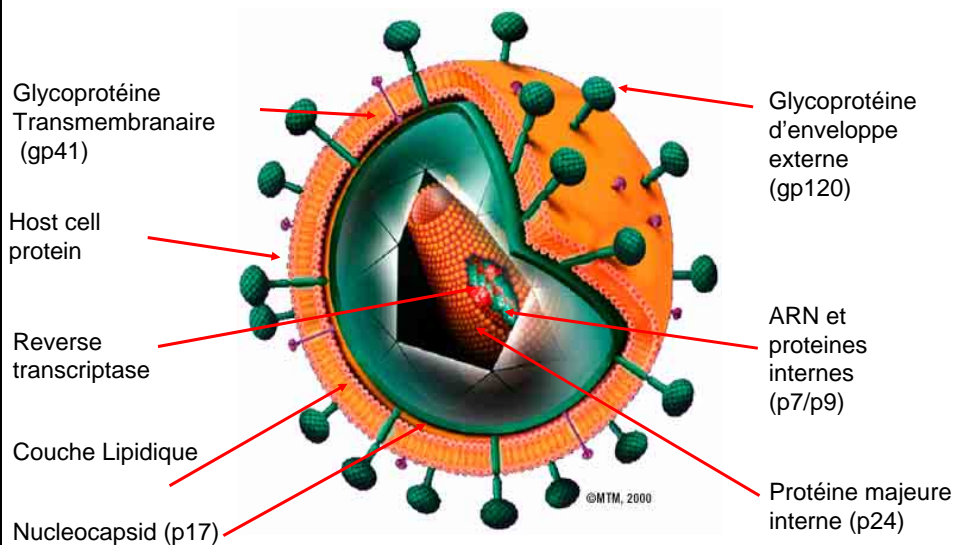
Vincent CALVEZ MD, PhD

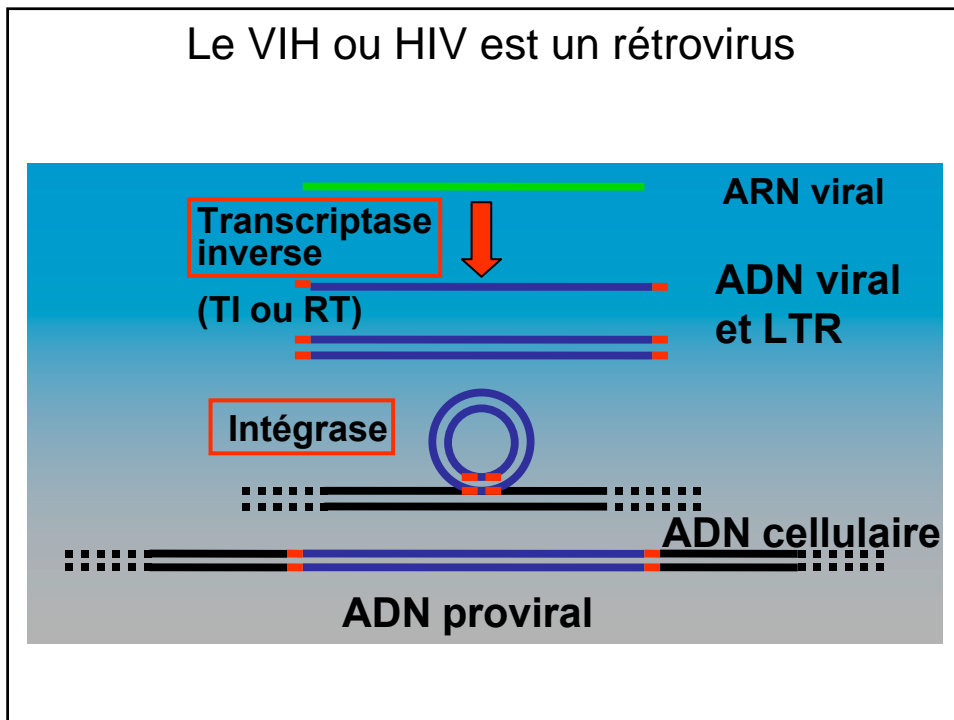
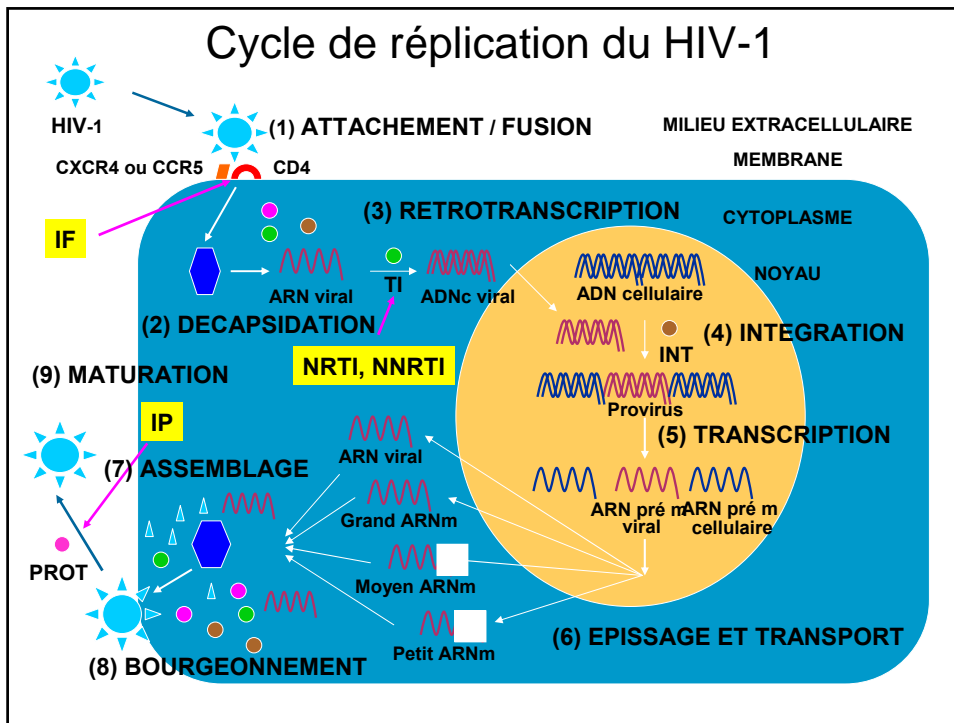
Dpt of Virology

Pitié-Salpêtrière Hospital

Paris, France

Virus de l'immunodéficience humaine

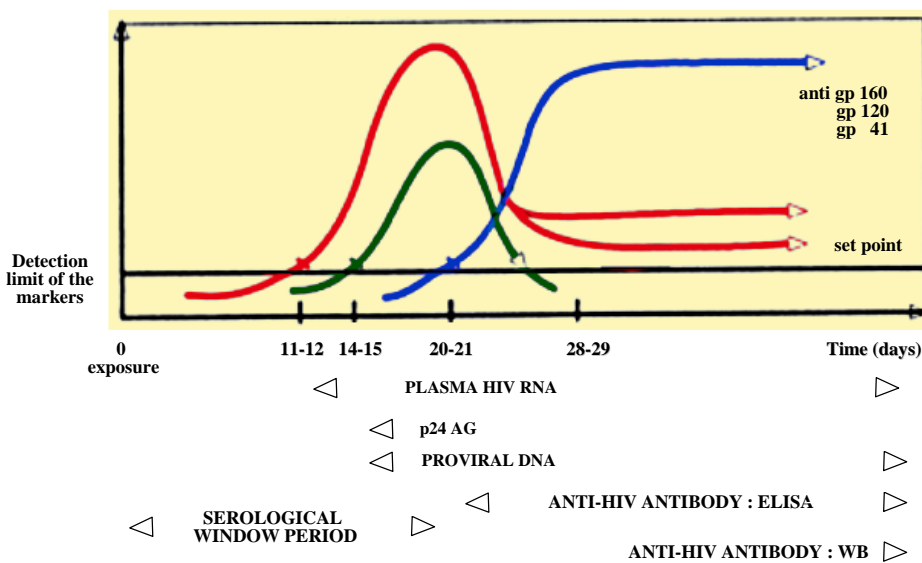


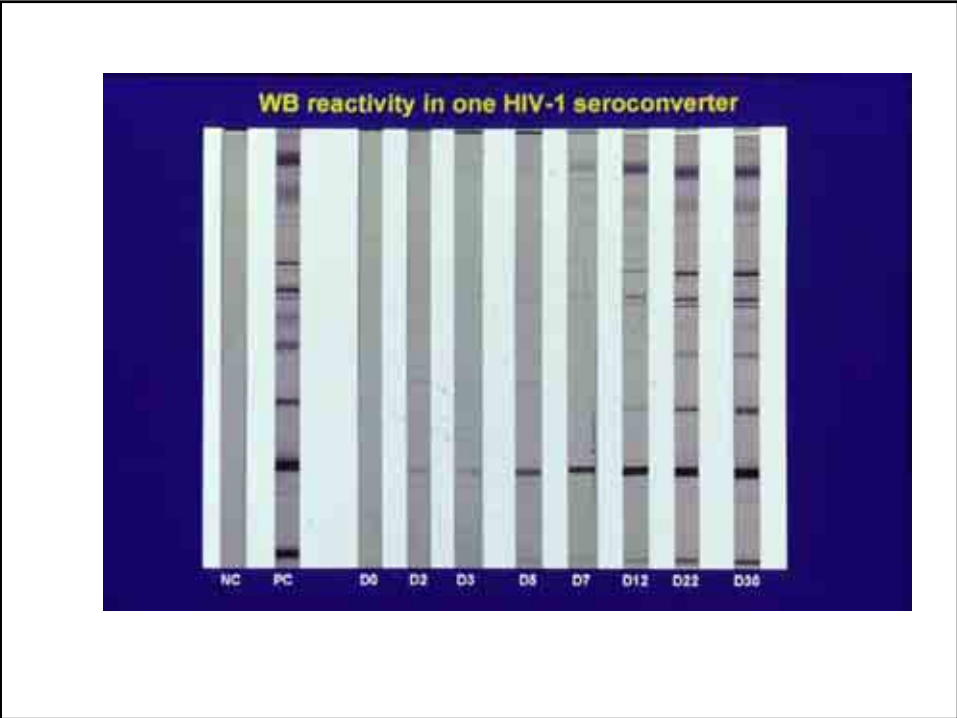
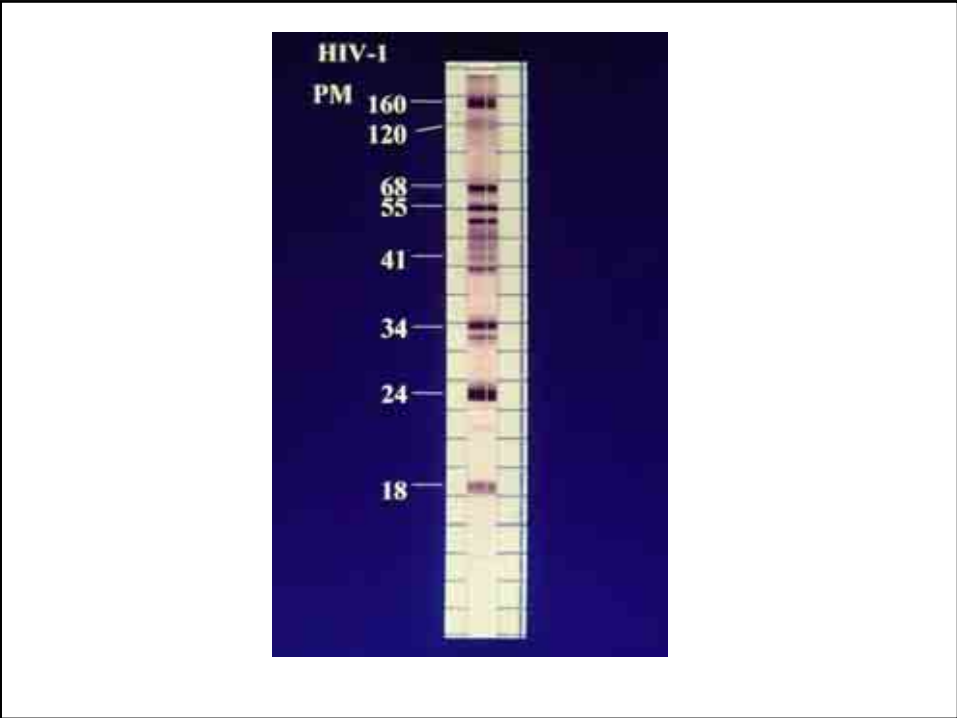


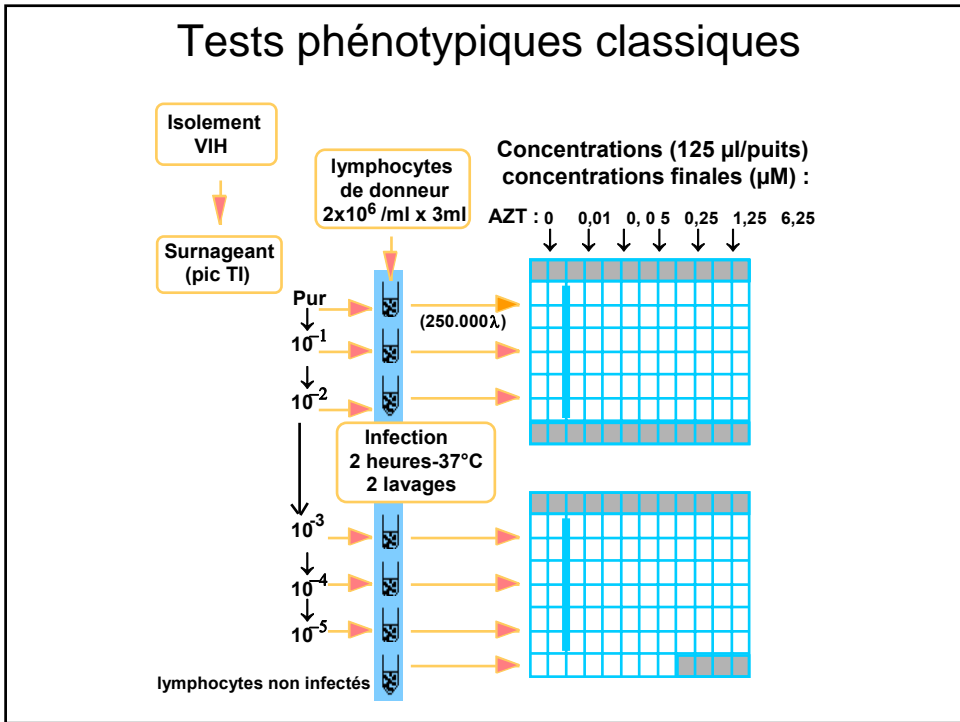
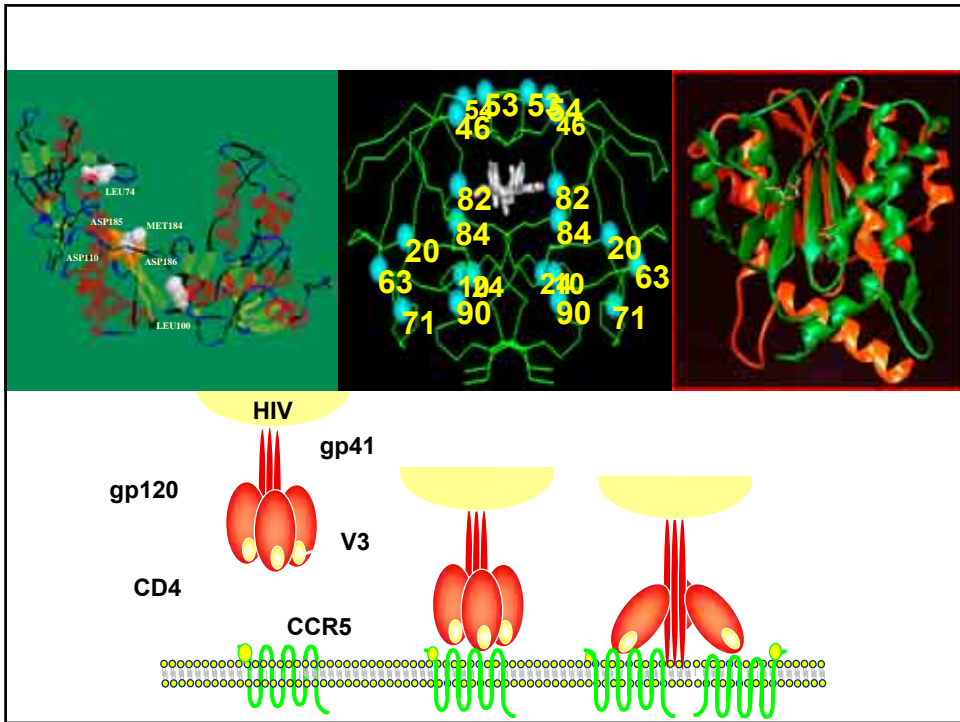
Diversité des VIH : Causes

- Erreur de la RT:
 - dépourvue de système de réparation
 - 1 erreur par cycle de réplication
- Dynamique importante de la réplication virale 10 milliards de virus produits /jour
- Recombinaisons multiples

Kinetics of viral markers during primary HIV-1 infection

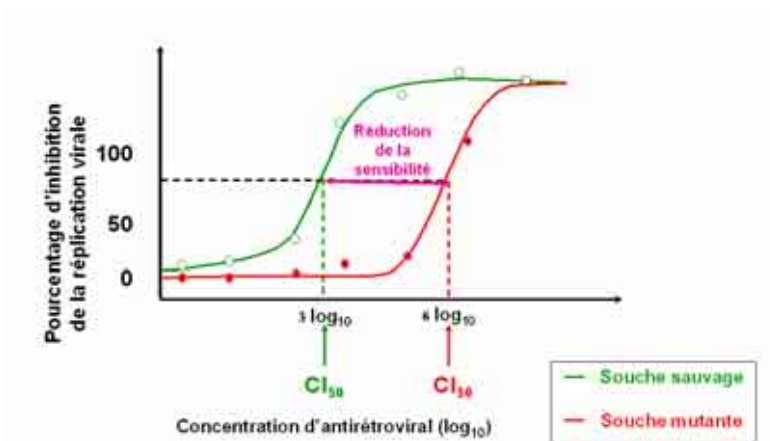






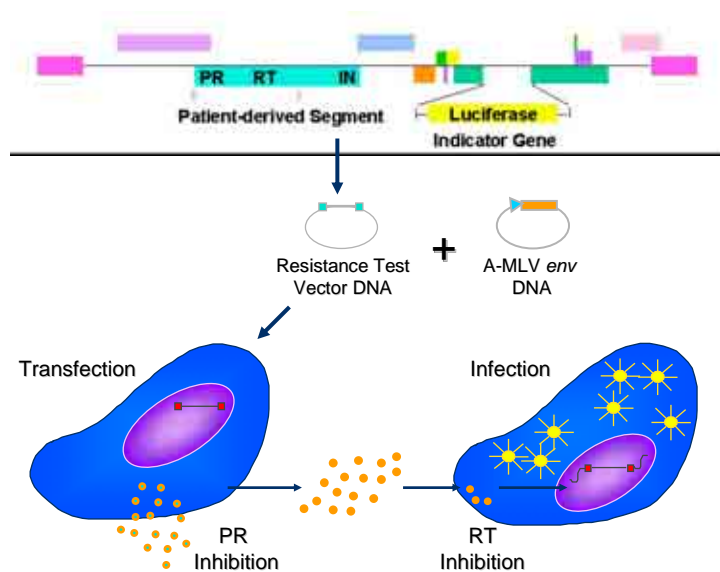
Relation concentration/effet avec les antirétroviraux : résistance et CI_{50}

Les médicaments du SIDA



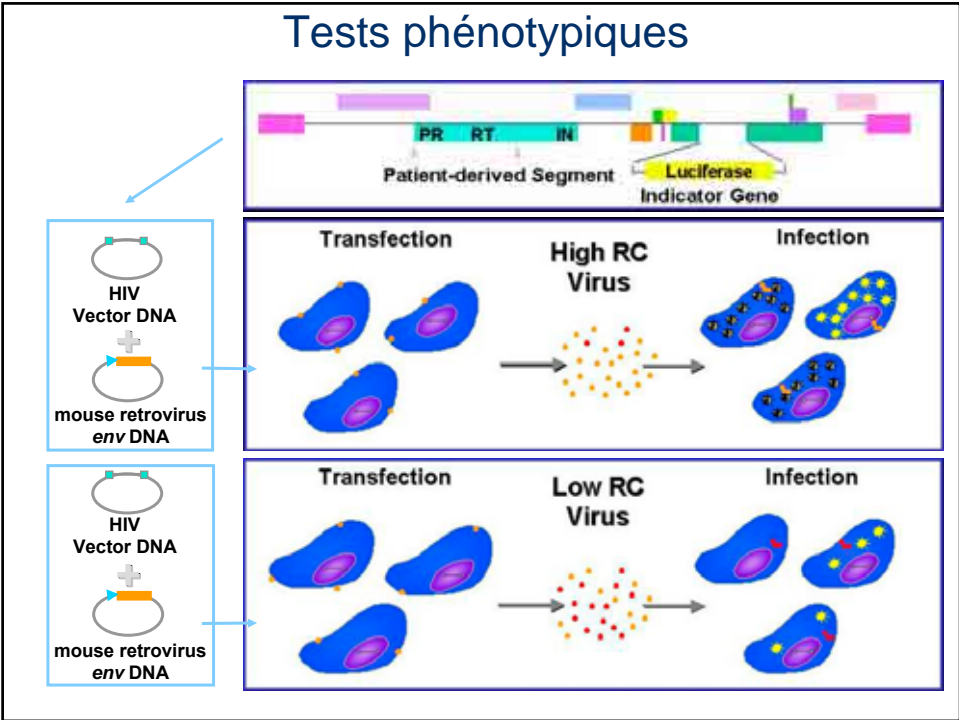
Adapted from Wilson, AIDS Read 2000 ; 10 :469.

Resistance Test Vector DNA

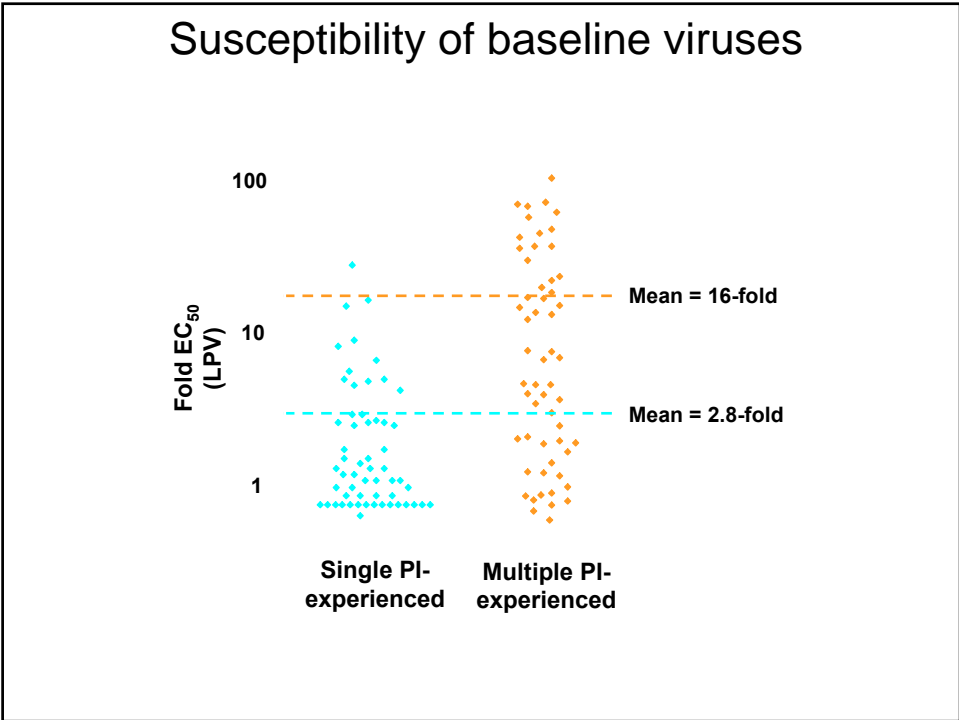


Richman, 11/99

Tests phénotypiques



Susceptibility of baseline viruses



A ONE YEAR RANDOMIZED CONTROLLED TRIAL OF
 GENOTYPIC VERSUS GENOTYPIC PLUS PHENOTYPIC
 RESISTANCE TESTING TO GUIDE ANTIRETROVIRAL
 THERAPY (THE ERA TRIAL MRC)

C Loveday IAS 2003

Primary Endpoint

Change in VL at 12 months from Baseline

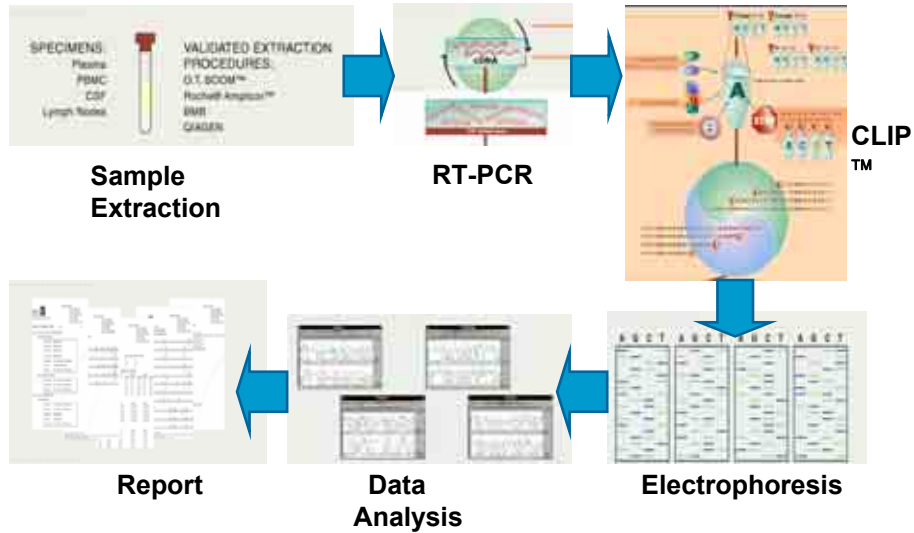
ARM	n	mean (SE)	Diff (SE)
GENO	136	-1.37 (0.2)	0.08 (0.27)*
GENO+PHENO	147	-1.28 (0.19)	

*p = 0.77 (NS)

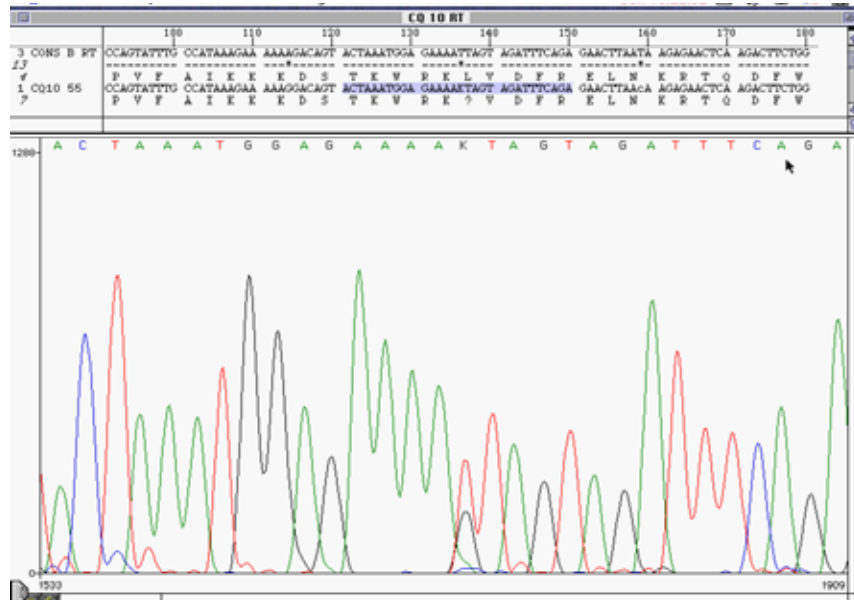
Proportion with VL <50c/ml at 12 months

ARM	n	Percent. with VL <50c/ml
GENO	136	35
GENO+PHENO	147	27 (NS)

TruGene™ HIV-1 Genotyping Technology*



* In North America: For research use only. Not for use in diagnostic procedures



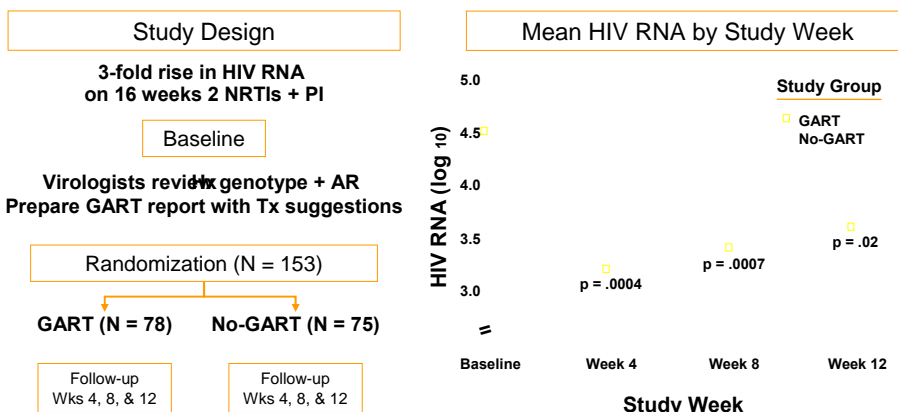
- Codon : Sauvage / Muté / Mixte

Retrospective resistance studies

- Baseline resistance predicts virological response independently of other variables such as VL at baseline and treatment history (Lac Majeur 1998)
 - Ait-Khaled et al: response to EFV/ABC/APV
 - Call et al: phenotype and response to salvage therapy
 - Calvez et al: ANRS ALTIS 2: response to d4T/3TC
 - Deeks et al: four-drug salvage therapy after PI failure
 - Hammer et al: ACTG 372: response to ABC/NFV/EFV/ADV
 - Harrigan et al: response to RTV/SQV
 - Lanier et al: response to ABC
 - Miller et al: response to ZDV/3TC
 - Para et al: response to IDV or SQV Sgel after SQV
 - Zolopa et al: response to SQV/RTV

CPCRA GART STUDY (046)

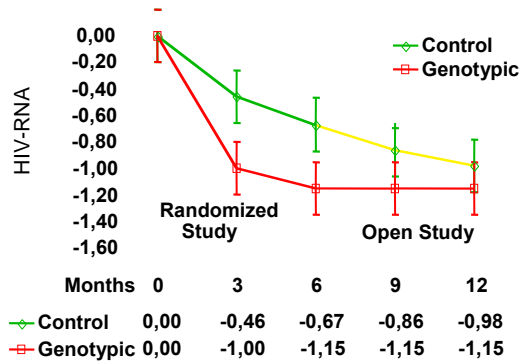
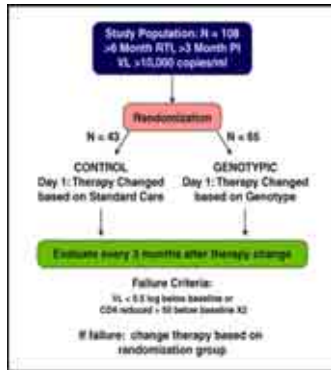
- A Pilot Study of the Short-Term Effects of Antiretroviral Management Based on Plasma Genotypic Antiretroviral Resistance Testing (GART) in Patients Failing Antiretroviral Therapy



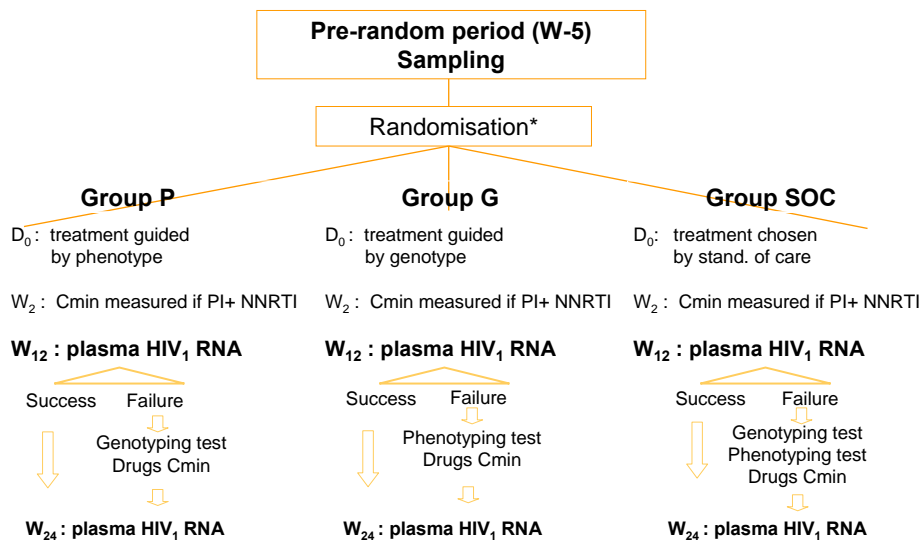
Improving HIV Therapy with Drug Resistance Genotyping

- **The VIRADAPT study**

- J .Durant¹, P .Clevenbergh¹, P.Halfon², P.Delgiudice¹, S.Porsin¹, P.Simonet³, N.Montagne³, E.Dohin⁴ and P. Dellamonica¹.

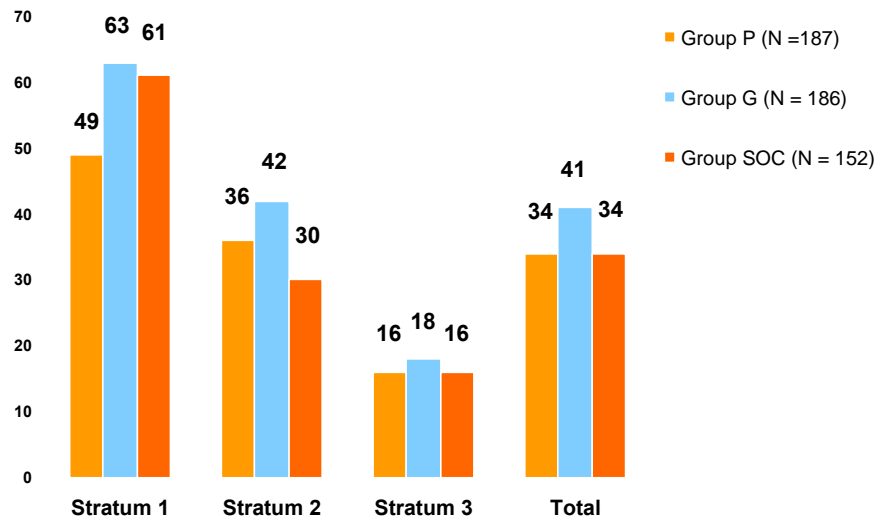


Trial design



* stratification : VL; previous ARV exposure

Figure 2 : Plasma HIV1RNA at Week 12
(% < 200 copies/ ml)



Predictive factors for virological response in patients
included in the Narval trial (ANRS 088)

Vray M. INSERM EMI 0214

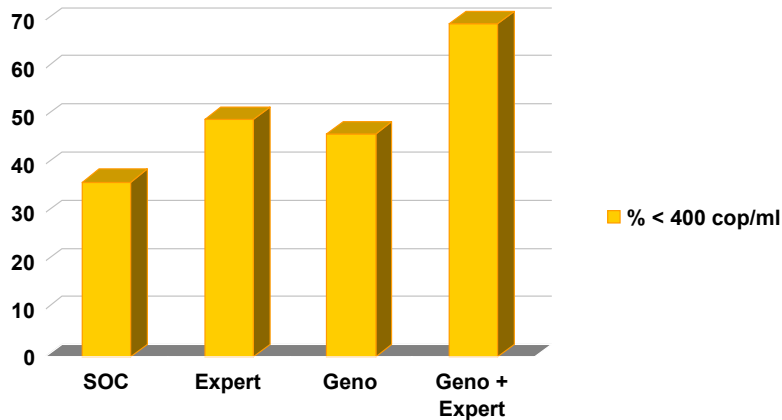
Final Multivariate Model (p<0.05)

Variables	OR (CI 95%)	p
Efavirenz in naive patients (Yes/no)	4.37 (2.76-6.9)	<0.001
Arm P versus SOC	1.14 (0.65-2.01)	0.652
G versus SOC	2.13 (1.2-3.79)	0.01
Lamivudine prescribed (Yes/no)	1.69 (1.01-2.83)	0.044
Abacavir in naive patients (Yes/no)	1.66 (1.02-2.72)	0.043
prior PI exposure (≥30 /<30 months)	0.64 (0.41-0.99)	0.046
Number of NAM (≥ 3/<3)	0.61 (0.39-0.97)	0.037
Number of PI mutations (≥ 5/<5)	0.42 (0.26-0.66)	<0.001
Plasma HIV-1 RNA (log)	0.37 (0.28-0.50)	<0.001
Nelfinavir prescribed (Yes/no)	0.30 (0.13-0.68)	0.004

Havana

- Salvage therapy based on:
 - Genotypic testing
 - Geno + expert advice
 - Expert advice
 - Standard of care
- Expert advice = clinicians + virologists

Havana results



ANRS AC 11 : GROUPE RESISTANCE INTERPRÉTATION DU GENOTYPE : ANALOGUES NUCLEOSIDIQUES ET NUCLEOTIDIQUES : VERSION 10; 0902

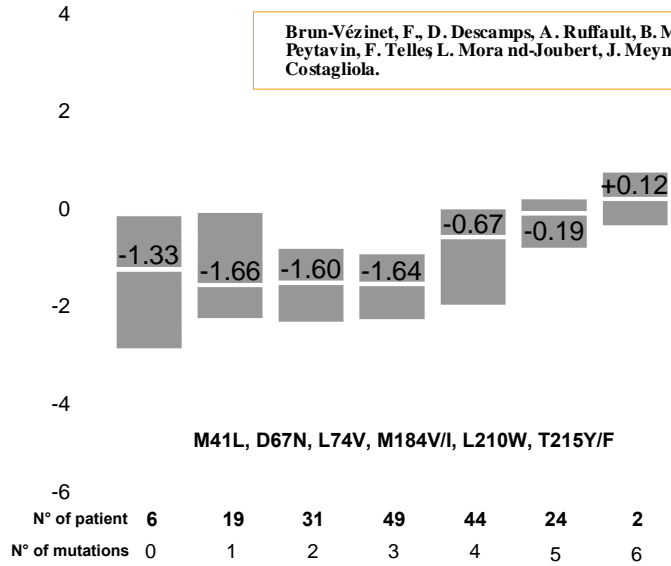
	Mutations associées à la résistance	Mutations associées à une «résistance possible»
AZT	<ul style="list-style-type: none"> • T215Y/F • > 2 mutations parmi : M41L, D67N, K70R, L210W, T215D/C/S, K219Q/E • Q151M • Insertion au codon 69 	<ul style="list-style-type: none"> • T215D/C/S
3TC	<ul style="list-style-type: none"> • M184V/I • Insertion au codon 69 	<ul style="list-style-type: none"> • Q151M
ddI	<ul style="list-style-type: none"> • L74V • > 2 TAMs dont T215Y/F • Q151M • Insertion au codon 69 	<ul style="list-style-type: none"> • K65R
ddC	<ul style="list-style-type: none"> • Données insuffisantes pour établir des recommandations 	<ul style="list-style-type: none"> • Données insuffisantes pour établir des recommandations
d4T	<ul style="list-style-type: none"> • V75M/S/A/T • T215Y/F • 2 mutations parmi : M41L, D67N, K70R, L210W, T215D/C/S, K219Q/E • Q151M • Insertion au codon 69 	<ul style="list-style-type: none"> • L210W et au moins 2 parmi M41L, D67N, K70R, K219Q/E • T215D/C/S
ABC	<ul style="list-style-type: none"> • > 4 mutations parmi M41L, D67N, L74V, M184V/I, L210W, T215Y/F • K65R + L74V + Y115F + M184V/I • Q151M • Insertion au codon 69 	<ul style="list-style-type: none"> • 4 mutations parmi M41L, D67N, L74V, M184V/I, L210W, T215Y/F • K65R
TDF	<ul style="list-style-type: none"> • Insertion au codon 69 • 3 TAMs dont M41L ou L210W • K65R 	

TAMs = M41L, D67N, K70R, L210W, T215Y/F, K219Q/E

<http://www.hivfrenchresistance.org/>

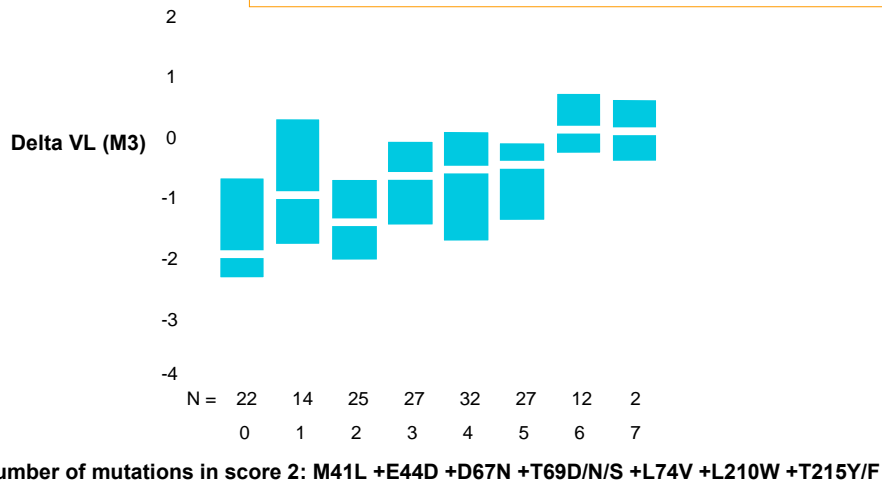
Clinically relevant interpretation of genotype for resistance to abacavir AIDS 2003

Brun-Vézinet, F., D. Descamps, A. Ruffault, B. Masquelier, V. Calvez, G. Peytavin, F. Telles L. Mora nd-Joubert, J. Meynard, M. Vray, and D. Costagliola.



Genotypic and pharmacological determinants of the virological response to tenofovir- including regimen in NRTI-experienced patients

B. Masquelier¹, C. Tamalet¹, B. Montès¹, D. Descamps¹, G. Peytavin, L. Bocket¹, M. Wirden¹, J. Izopet¹, V. Schneider¹, V. Ferré¹, A. Ruffault¹, P. Palmer¹, A. Trylesinski², M. Miller², F. Brun-Vézinet¹, D. Costagliola¹ and the ANRS AC11 Resistance study group



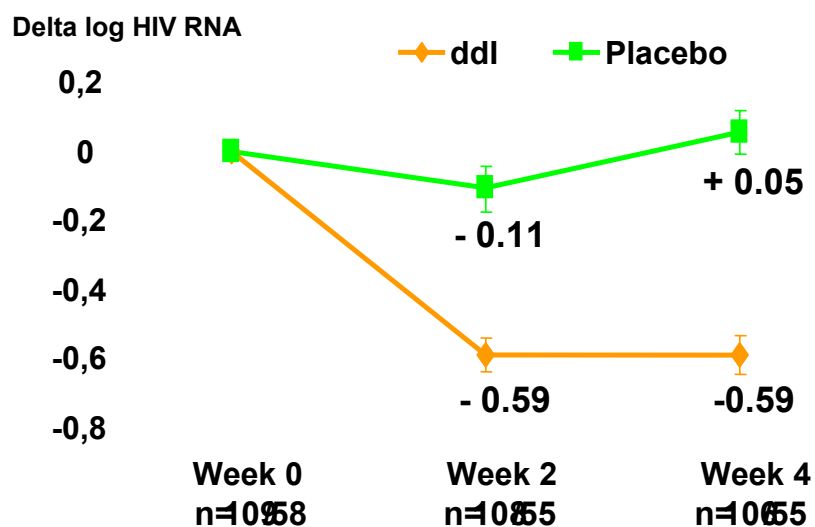
Clinically relevant interpretation of genotype for resistance to didanosine (VIDEX EC®) in treatment-experienced HIV-infected patients

AG Marcelin¹, JM Molina², P Flandre³,
A Gaudichet⁴, I Dujardin⁴, G Leleu⁴ and V Calvez¹
for the JAGUAR study group

¹Hopital Pitié-Salpêtrière, Paris, ²Hopital St-Louis, Paris,
³INSERM 472, Villejuif and ⁴Bristol-Myers Squibb, Rueil, France.

AAC in press

Mean Change in plasma HIV RNA from baseline (intent-to-treat analysis)



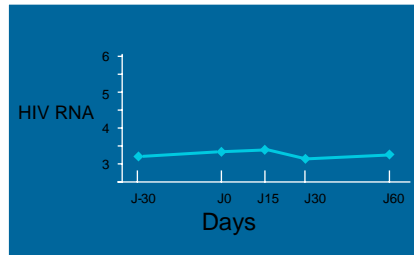
Mutations associated with negative impact on viral load decrease *Univariate analysis in ddi arm (p<0.20)*

		ddi		Placebo	
		n	median RNA change	n	median RNA change
M41L	Absent	52	- 0.87	24	+ 0.06
	Present	49	- 0.28	28	+ 0.07
D67N	Absent	66	- 0.66	32	+ 0.06
	Present	35	- 0.26	20	+ 0.07
T69D	Absent	92	- 0.61	48	+ 0.06
	Present	9	- 0.08	4	+ 0.12
L74V	Absent	92	- 0.61	49	+ 0.06
	Present	9	- 0.06	3	+ 0.20
L118I	Absent	82	- 0.61	42	+ 0.07
	Present	19	- 0.28	10	- 0.04
L210W	Absent	73	- 0.66	39	+ 0.07
	Present	28	- 0.34	13	+ 0.01
T215F/Y	Absent	46	- 0.89	21	+ 0.07
	Present	55	- 0.38	31	+ 0.01
K219E/Q	Absent	76	- 0.61	37	+ 0.08
	Present	25	- 0.44	15	+ 0.00

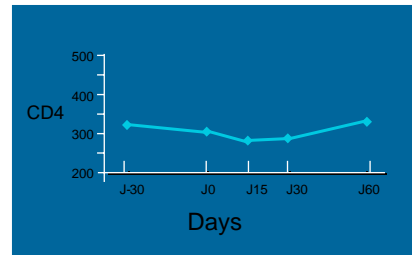
Mutations associated with positive impact on viral load decrease *Univariate analysis in ddi arm (p<0.20)*

		ddi		Placebo	
		n	median RNA change	n	median RNA
change					
M184V					
	Absent	8	- 0.15	6	- 0.23
	Present	93	- 0.60	46	+ 0.07
K70R					
	Absent	74	- 0.44	38	+ 0.05
	Present	27	- 0.94	14	+ 0.07

Soustractive study stopping only NNRTIs in patients with failure and stable HIV RNA and harboring NNRTIs mutated viruses



Stop NNRTI

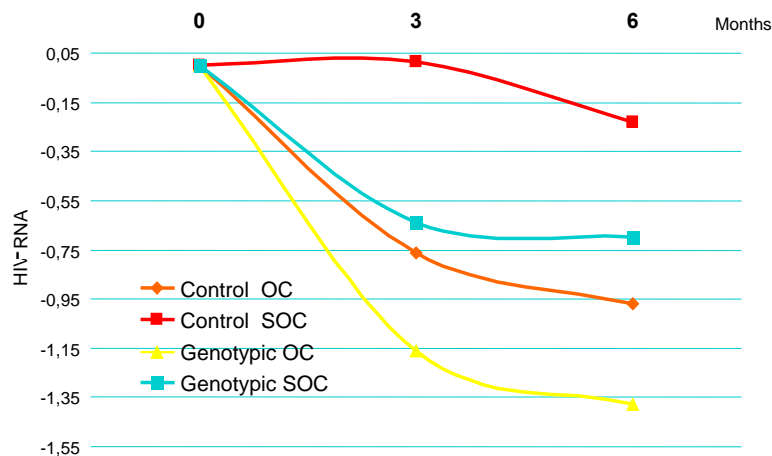


Stop NNRTI

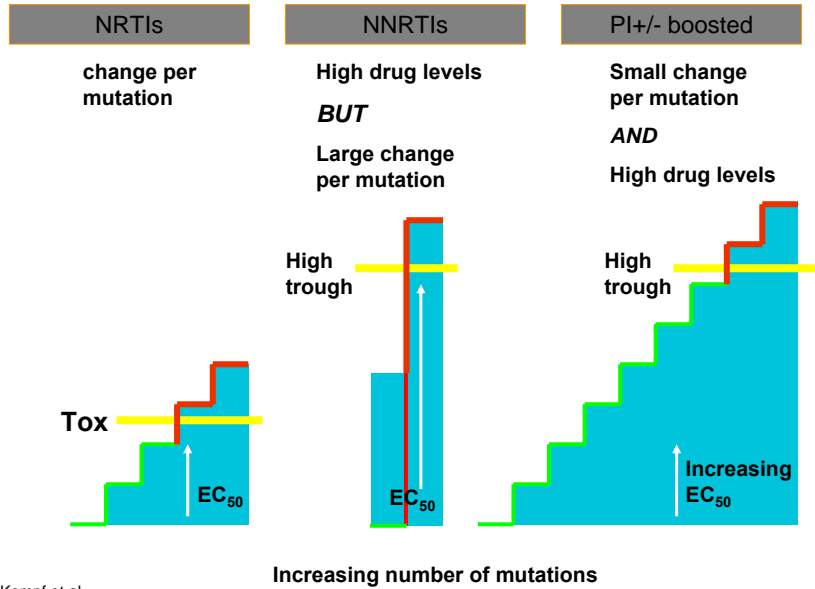
Marc WIRDEN, Anne SIMON, Luminita SCHNEIDER, Roland TUBIANA, Luc PARIS, Anne Genevieve MARCELIN, Constance DELAUGERRE, Mayeule LEGRAND, Serge HERSON, Gilles PEYTAVIN, Christine KATLAMA and Vincent CALVEZ.

Journal of Clinical Microbiology, 2003; 41 (6): 2713-2715

Efficacy analysis based on drug levels and randomization arm

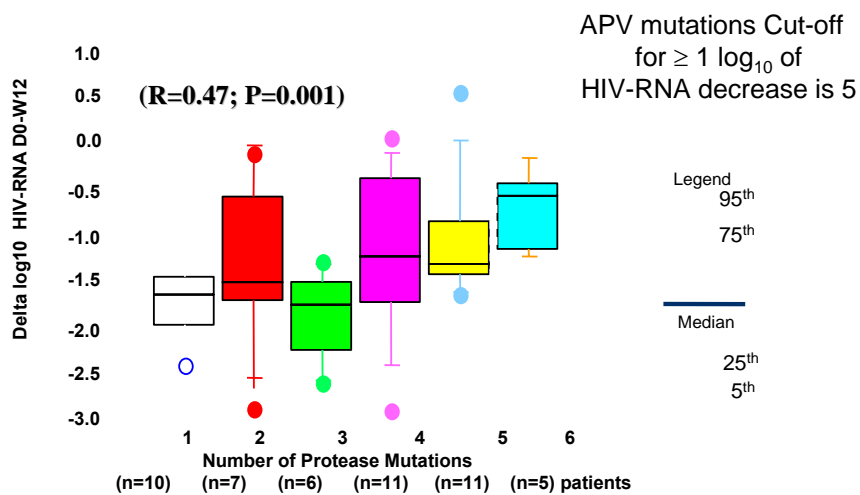


Barriers to resistance: PK and genetics

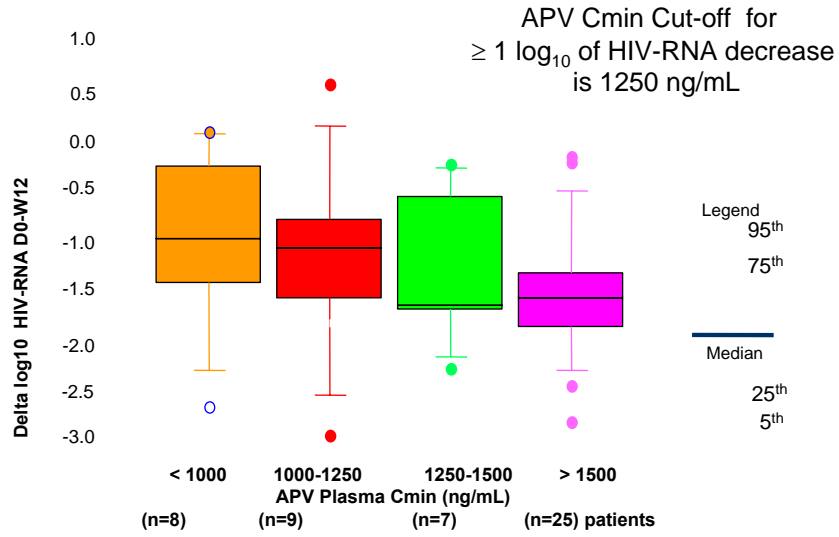


Dale Kempf et al.

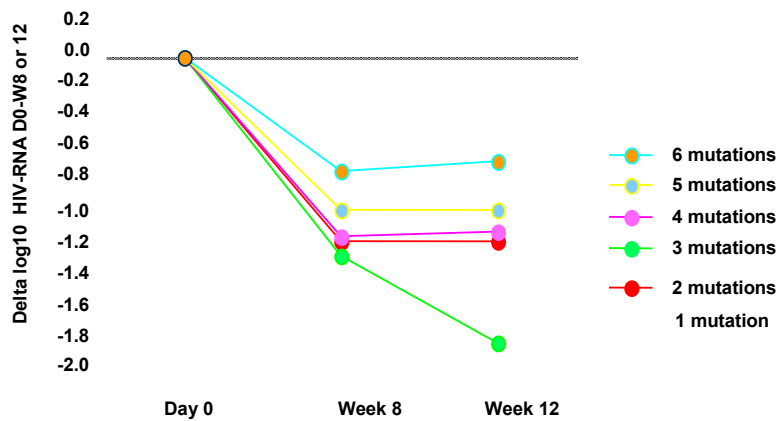
Predictivity of APV Key mutations on the treatment efficacy (Delta of Plasma HIV RNA between baseline and weeks 12)



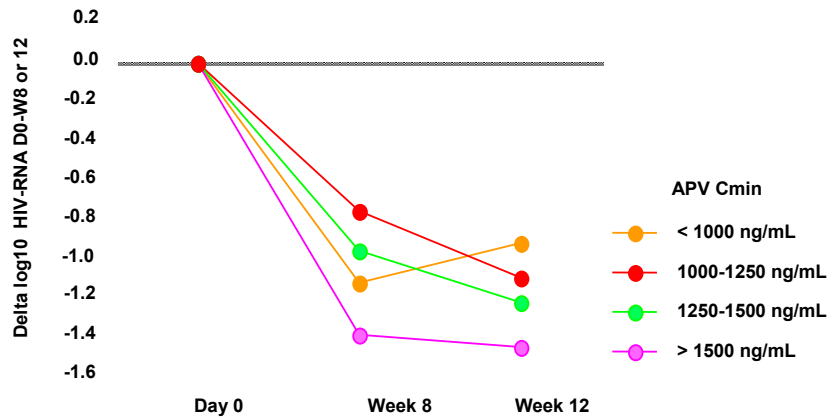
Predictivity of APV Cmin on the treatment outcome (Delta of Plasma HIV RNA between baseline and weeks 12)



Relationship between number of “APV mutations” and Delta of Plasma HIV RNA at week 8 and week 12



Relationship between APV Cmin and Delta of Plasma HIV RNA at week 8 and week 12



Genotypic Inhibitory Quotient (GIQ)

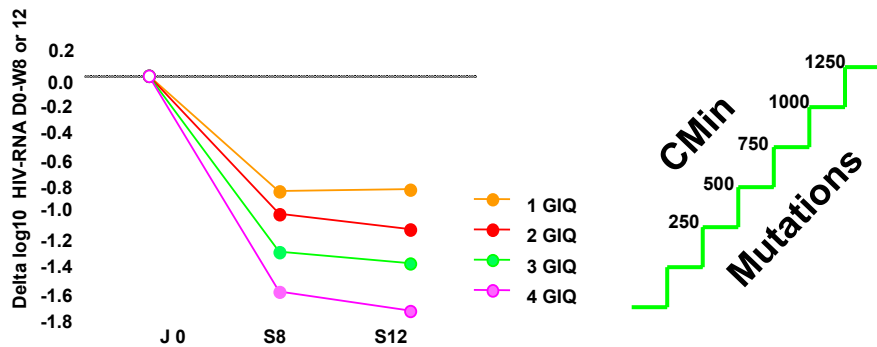
$$\text{GIQ} = \frac{\text{Cmin,ss associated with } \geq 1 \log_{10} \text{ of HIV-RNA decrease}}{\text{No Protease mutations associated with } \geq 1 \log_{10} \text{ of HIV-RNA decrease}}$$

→ For APV, the GIQ associated with $\geq 1 \log_{10}$ of HIV-RNA decrease = $\frac{1250}{5}$

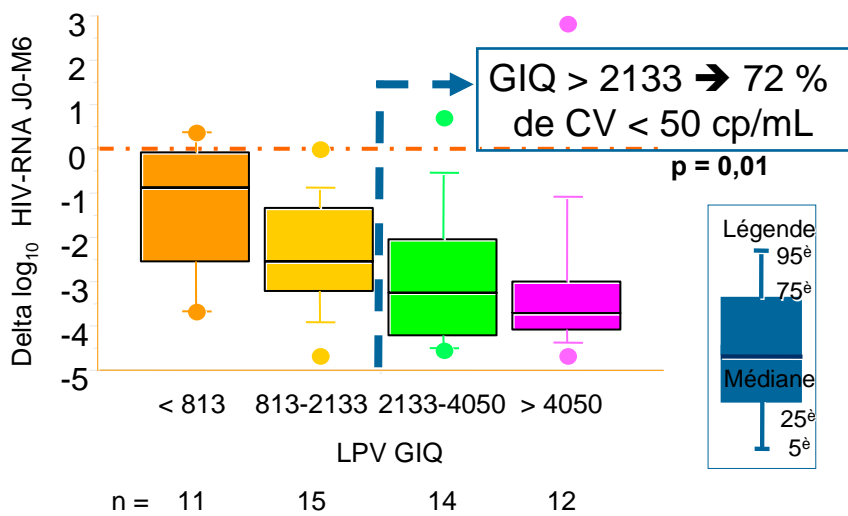
→ Considering APV Cmin and the number of Protease mutations at baseline, patients were classified as having 1 x GIQ, 2 x GIQ, 3 x GIQ or 4 x GIQ.

Genotypic inhibitory quotient (GIQ) r/APV 100mg/600mg BID AG Marcelin et al, AAC 2003

- 1 unit of GIQ = $\frac{C_{min} \text{ S8 APV}}{\text{Nb of mutations at baseline}}$
- 1 unit of GIQ = $\frac{1250}{5} = 250$



Prédictibilité de la réponse antivirale au Lopinavir à M6 par le Quotient Inhibiteur Génotypique



Cabié A et al., XV International AIDS Conference 2004, TuPeB4620

Virological and Pharmacological Parameters Predicting the Response to Lopinavir/ritonavir in Heavily Protease Inhibitor Experienced Patients

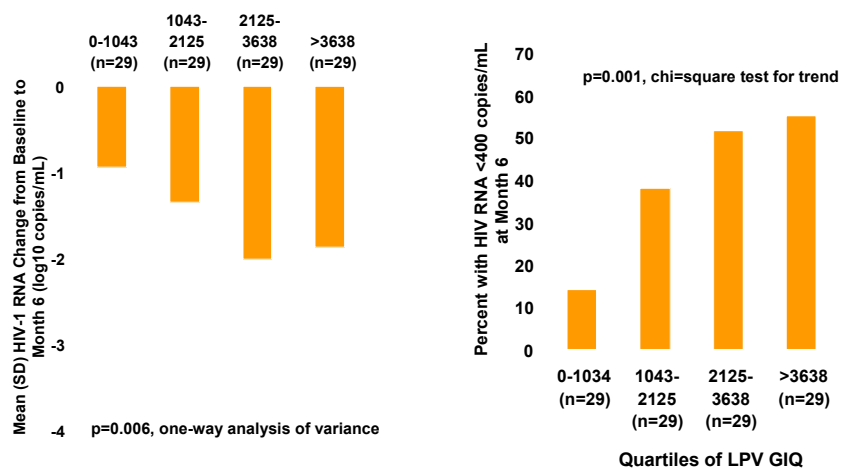
Anne-Geneviève Marcelin¹, Isabelle Cohen-Codar², Martin S. King³, Philippe Colson⁴, Emmanuel Guillevic², Diane Descamps⁵, Claire Lamotte⁶, Véronique Schneider⁷, Jacques Ritter⁸, Michel Segondy⁹, Héléne Peigue-Lafeuille¹⁰, Laurence Morand-Joubert¹¹, Anne Schmuck¹², Annick Ruffault¹³, Pierre Palmer¹⁴, Marie-Laure Chaix¹⁵, Vincent Mackiewicz¹⁶, Véronique Brodard¹⁷, Jacques Izopet¹⁸, Jacqueline Cottalorda¹⁹, Evelyne Kohli²⁰, Jean-Pierre Chauvin², Dale J. Kempf³, Gilles Peytavin⁶, Vincent Calvez¹

AAC 2004, *in press*

- The aim of this study was to evaluate the predictivity of the GIQ in 116 PI-experienced patients treated by lopinavir/ritonavir (LPV/r).
- The overall decrease in HIV-1 RNA from baseline to month 6 was a median of -1.50 log₁₀ copies/mL and 40% of patients had plasma HIV-1 RNA below 400 copies/ml at month 6.

HIV-1 RNA mean change from baseline to month 6 and proportion of patients with HIV-1 RNA <400 copies/mL at month 6 by quartiles of lopinavir genotypic inhibitory quotient

Quartiles of LPV GIQ

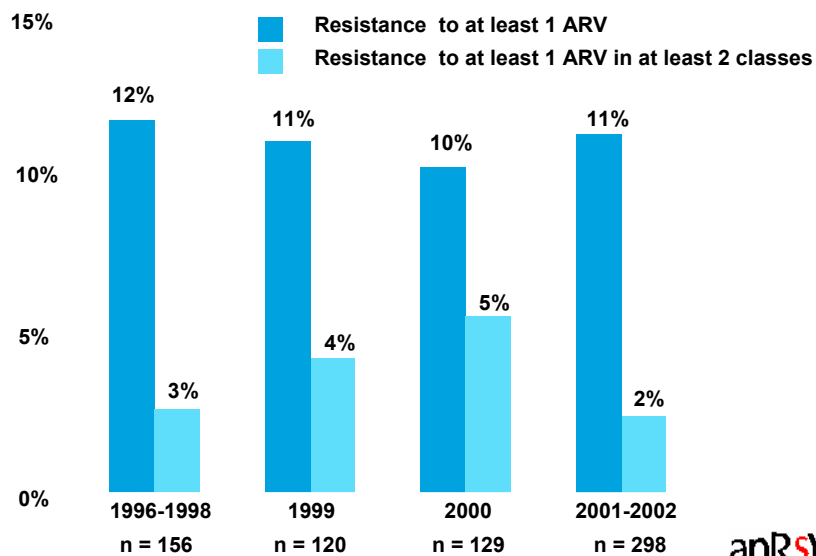


LPV, lopinavir; GIQ, genotypic inhibitory quotient; SD, standard deviation

Effects of baseline and pharmacologic characteristics on HIV-1 RNA change from baseline among all patients and patients with 3 or more baseline PI mutations

Variable	All patients		Patients with 3 or more PI mutations	
	p-value (simple linear regression)	p-value (multiple linear regression)	p-value (simple linear regression)	p-value (multiple linear regression)
Number of LPV mutations	0.001	ns	0.25	-
LPV Cmin	0.47	-	0.06	ns
log ₁₀ LPV GIQ	0.001	0.008	0.03	0.04
Baseline HIV-1 RNA	0.10	0.04	0.32	-
Baseline CD4 count	0.59	-	0.29	-
Number of prior PIs	0.004	0.04	0.17	-
number of active NRTIs	0.17	-	0.46	-
NNRTI use in an NNRTI-naive patient	0.05	ns	0.06	0.09
CDC class C status	0.27	-	0.18	-
Gender	0.58	-	0.36	-
Age	0.05	ns	0.56	-

Evolution of the frequency of resistant HIV-1 strains in primary infection from 1996 to 2002



Harzic et al. AIDS 2002, Chaix et al. AIDS in press



Résistance génotypique - Patient index/source A

		PROTEASE MUTATIONS										REVERSE TRANSCRIPTASE MUTATIONS													
Sample	Specimen	Bulk	L	L	M	I	L	A	V	V	I	L	M	E	D	T	K	V	V	Y	M	L	T	K	
date	P/C#	No clones (%)	33	46	54	63	71	77	82	84	90	41	44	67	69	103	108	118	181	184	210	215	219		
PHI - A																									
Source patient A	nov-2000	P	Bulk	I	F	L	V	P	V	-	T	V	M	L	D	N	D	-	I	I	-	V	W	Y	R
			16/16 (100%)	I	F	L	V	P	V	-	T	V	M	L	D	N	D	-	I	I	-	V	W	Y	R
Index patient A	jan-2001	P	Bulk	I	F	L	V	P	V	-	T	V	M	L	D	N	D	-	I	I	-	V	W	Y	R
			17/17 (100%)	I	F	L	V	P	V	-	T	V	M	L	D	N	D	-	I	I	-	V	W	Y	R
	may-2002	P	Bulk	I	F	L	V	P	V	-	T	V	M	L	D	N	D	N	-	I	-	-	W	D	R
			4/7 (60%)	I	F	L	V	P	V	-	T	V	M	L	D	N	D	-	I	I	-	-	W	D	-
			3/7 (40%)	I	F	L	V	P	V	-	-	V	M	L	D	N	D	N	-	I	-	-	W	D	R
	jan-2003	P	Bulk	I	F	L	V	P	V	-	A/S/T	V	M	L	D	N	D	-	I	I	-	-	W	D	R
		C	Bulk	I	F	L	V	P	V	-	A	V	M	L	D	N	D	-	I	-	-	-	W	D	R

C Delaugerre, Antivir ther, in press



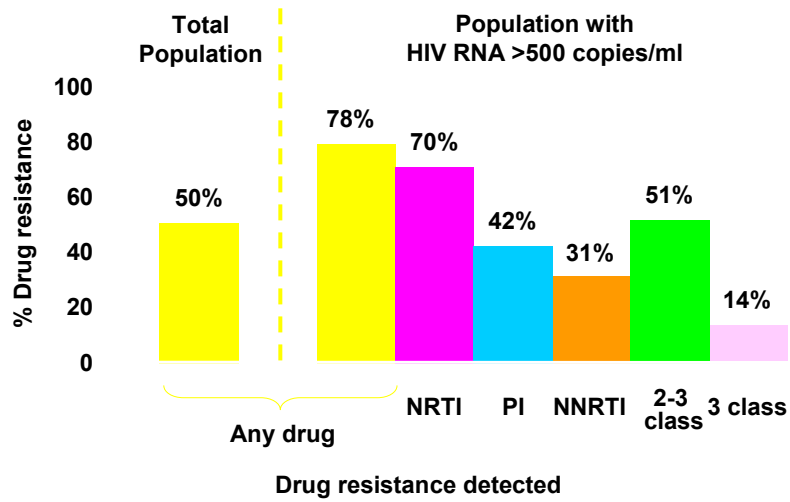
Résistance génotypique - Patient index/source B

		PROTEASE MUTATIONS										REVERSE TRANSCRIPTASE MUTATIONS													
Sample	Specimen	Bulk	L	L	M	I	L	A	V	V	I	L	M	E	D	T	K	V	V	Y	M	L	T	K	
date	P/C#	No clones (%)	33	46	54	63	71	77	82	84	90	41	44	67	69	103	108	118	181	184	210	215	219		
PHI - B																									
Source patient B	dec-1999	P	Bulk	V	-	I	-	P	T	I	-	V	M	-	-	N	D	N	-	I	C	V	-	L	Q
			21/21 (100%)	V	-	I	-	P	T	I	-	V	M	-	-	N	D	N	-	I	C	V	-	L	Q
Index patient B	jan-2000	P	Bulk	V	-	I	-	P	T	I	-	-	M	-	-	N	D	N	-	I	C	-	-	L	Q
			16/17 (94%)	V	-	I	-	P	T	I	-	-	M	-	-	N	D	N	-	I	C	-	-	L	Q
			1/17 (6%)	V	-	I	-	P	T	I	-	-	M	-	-	N	D	-	-	I	C	-	-	L	Q
	jan-2002	P	Bulk	V	-	-	-	P	T	I	-	-	M	-	-	N	D	N	-	I	C	-	-	L	Q
			7/7 (100%)	V	-	-	-	P	T	I	-	-	M	-	-	N	D	N	-	I	C	-	-	L	Q
	dec-2002	P	Bulk	V	-	-	-	P	T	I	-	-	M	-	-	N	D	N	-	I	C	-	-	L	Q
		C	Bulk	V	-	-	-	P	T	I	-	-	M	-	-	N	D	N	-	I	C	-	-	L	Q

C Delaugerre, Antivir ther, in press

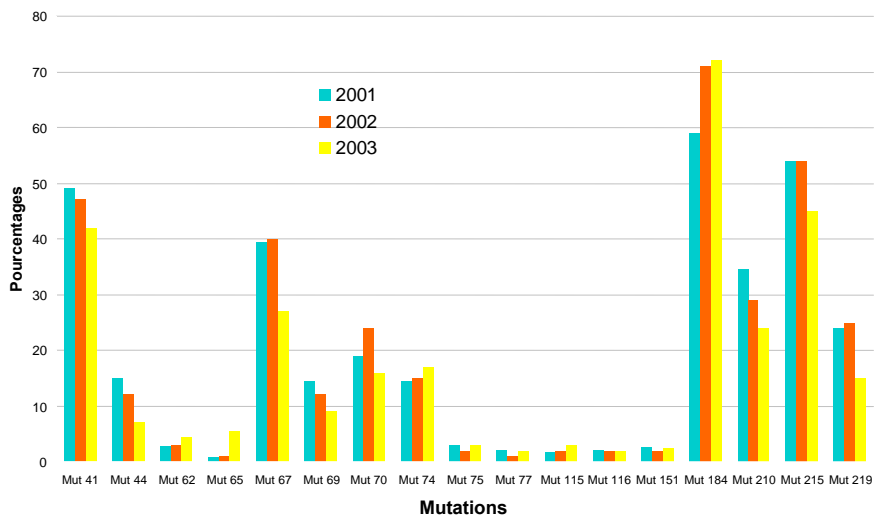


Viral resistance is an increasing problem



Richman D *et al.* 41st ICAAC, 2001, Chicago.
Abstract LB-17

Mutations NRTIs



AG Marcelin, M Wirden, C Delaugerre, V Calvez : Dpt of virology
R Tubiana, R Agher, C Katlama: HIV clinical research unit
A Simon, M Bonmarchand: Dpt of internal medicine
2003 Pitié-Salpêtrière hospital, Paris, France

Dpt of Virology

- Dr Anne-Geneviève Marcelin
- Dr Marc Wirden
- Dr Contance Delaugerre
- Dr Bahia Amelal
- Pr Vincent Calvez

HIV clinical research unit

- Dr Marc-Antoine Valantin
- Dr Roland Tubiana
- Dr Stéphanie Dominguez
- Dr Claudine Duvivier
- Dr Luminata Schneider
- Dr Hocine Aït Mohand
- Dr Rachid Agher
- Dr Jade Ghosn
- Pr Christine Katlama



Dpt of Immunology

- Pr Brigitte Autran
- Dr Guislaine Carcelain

Dpt of Internal Medicine

- Dr Manuela Bonmarchand
- Dr Anne Simon

Statistical analyses

- Dr Dominique Costagliola
- Dr Philippe Flandre

Dpt of clinical pharmacology (Bichat hospital)

- Dr Gilles Peytavin
- Dr Claire Lamotte

AC 5 : ANRS clinical trials

AC 11: ANRS medical Virology