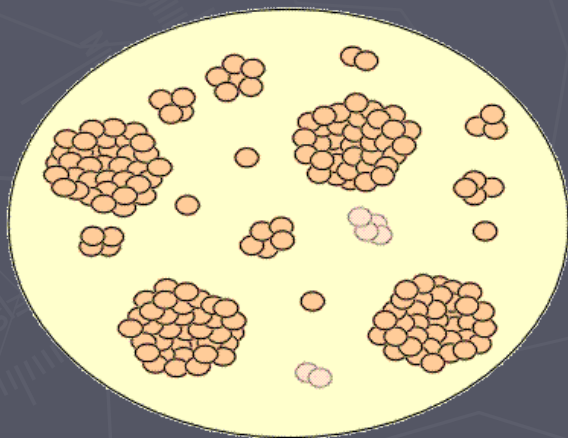
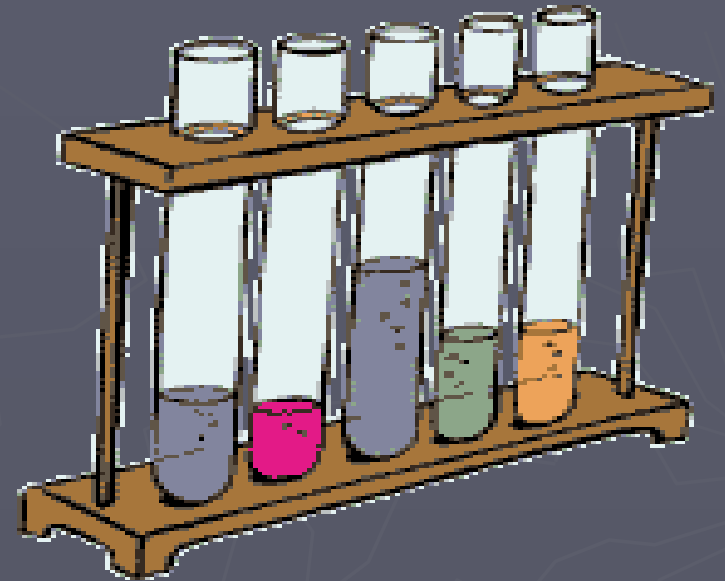


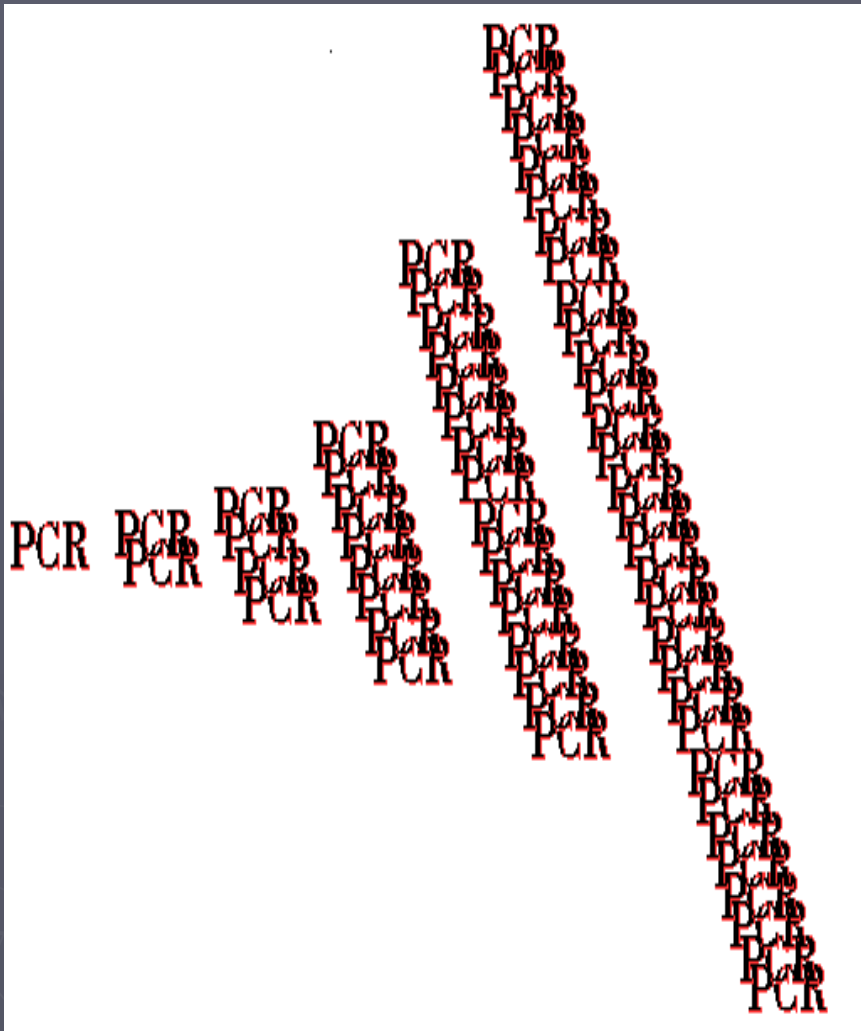
Optimisation des traitements antirétroviraux : de la chimie à l'alchimie

Méthodes : les outils biologiques et l'évaluation

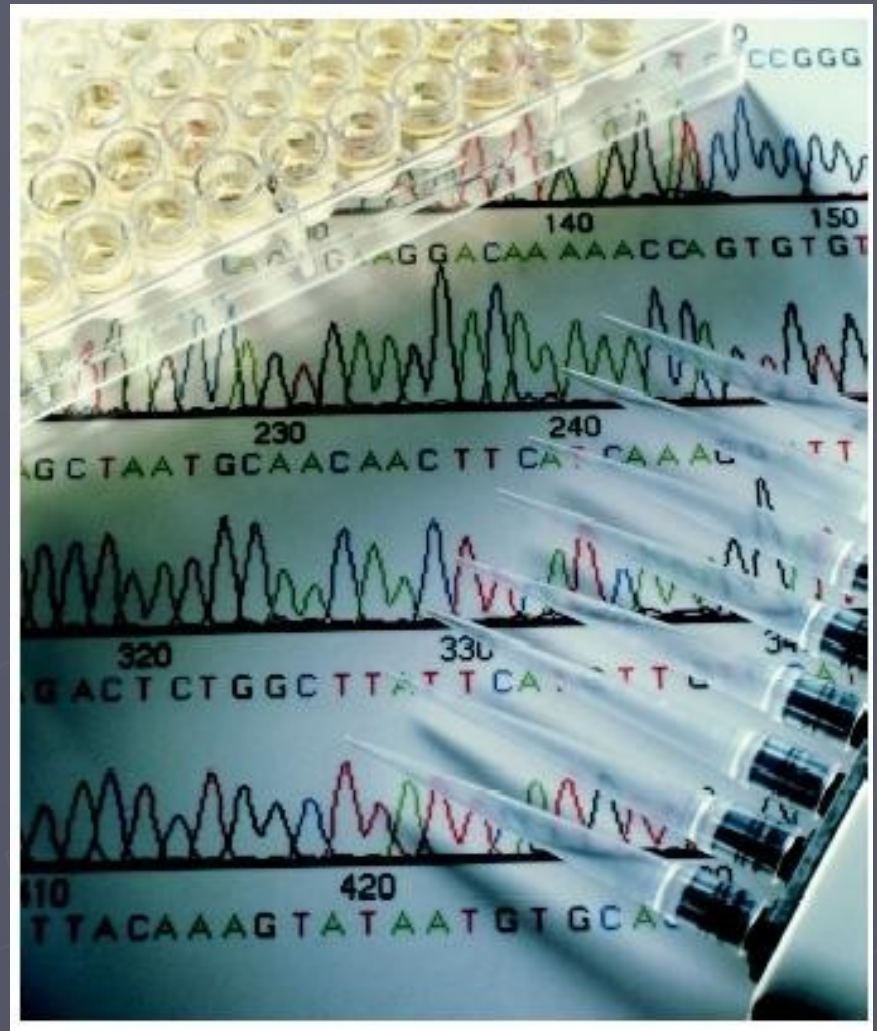
Dr JC TARDY , LYON

LES OUTILS du VIROLOGUE

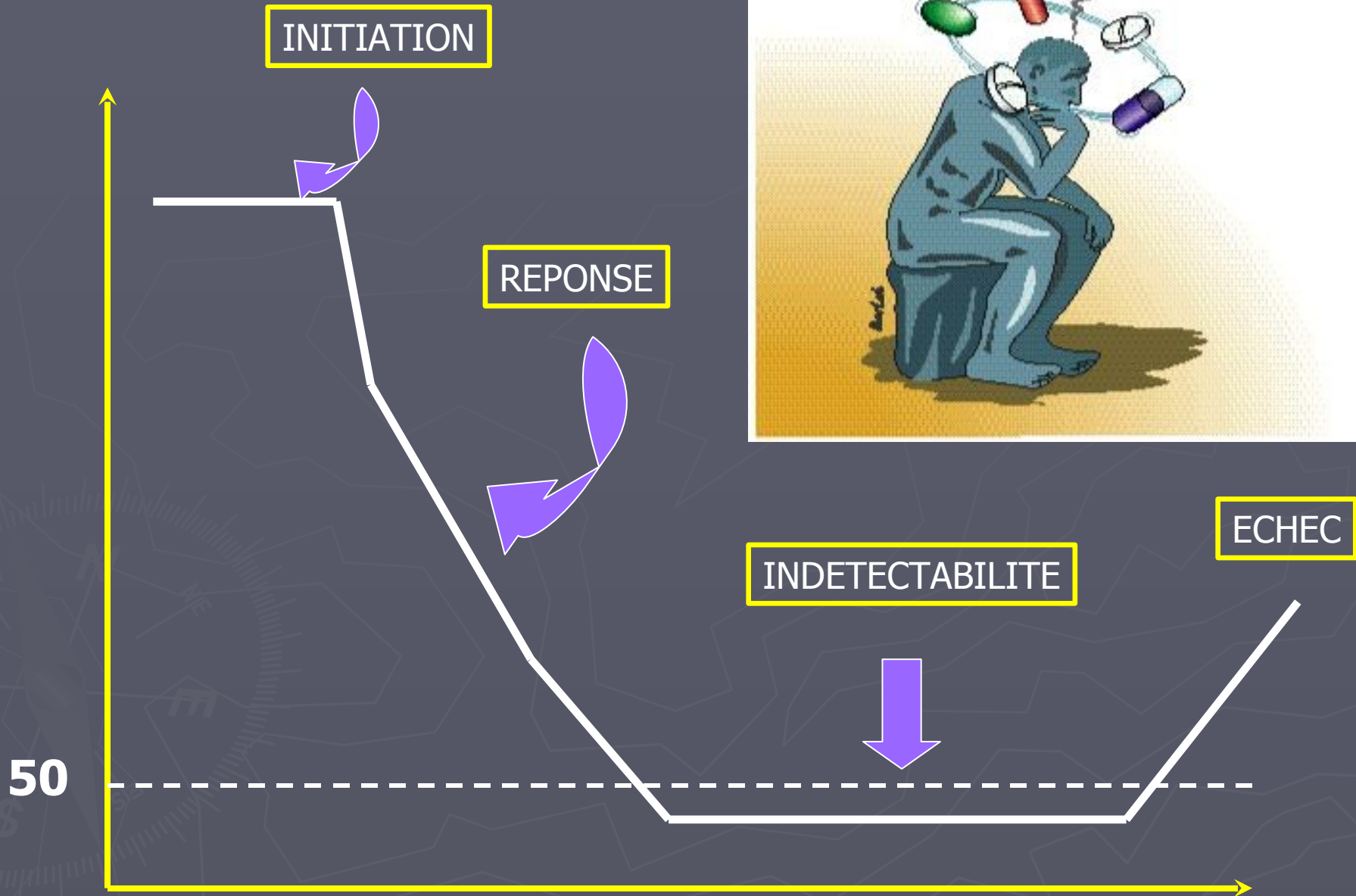




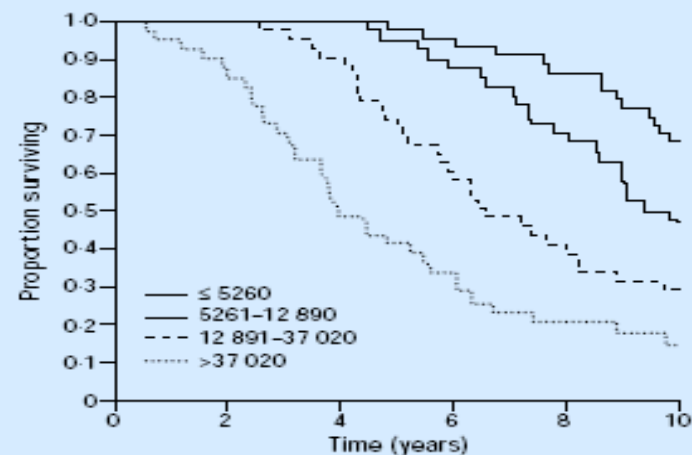
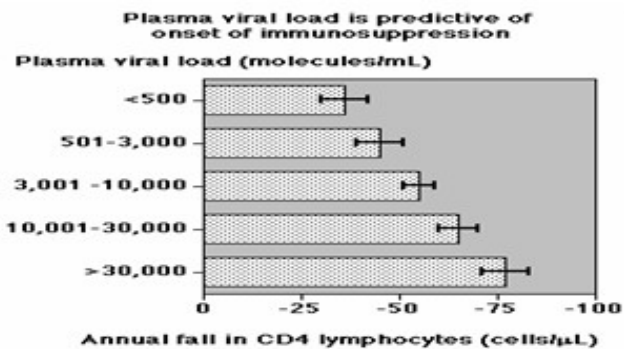
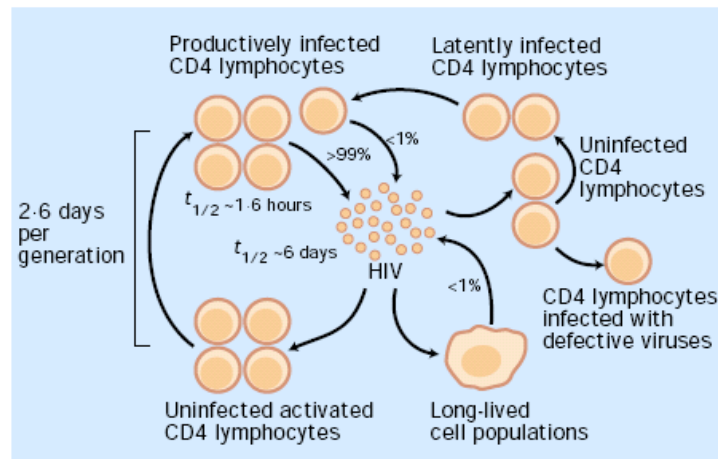
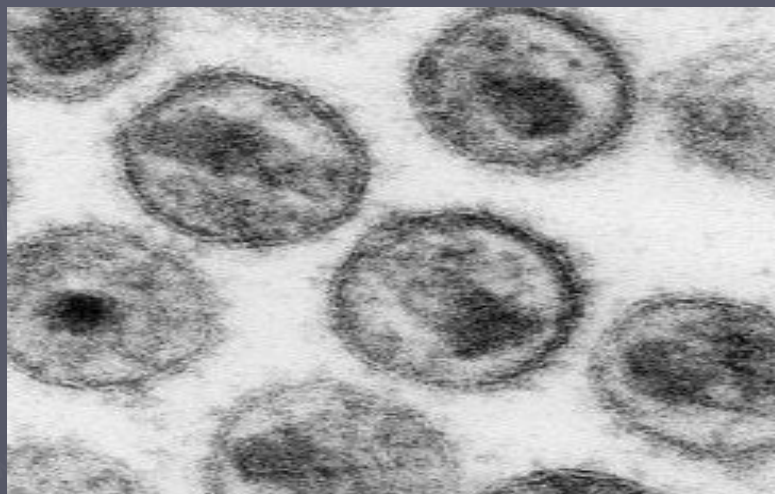
CHARGE VIRALE



SEQUENCAGE



DEBUTER UN TRAITEMENT ? LA CHARGE VIRALE



* CV > 5 Log (Recommandations)

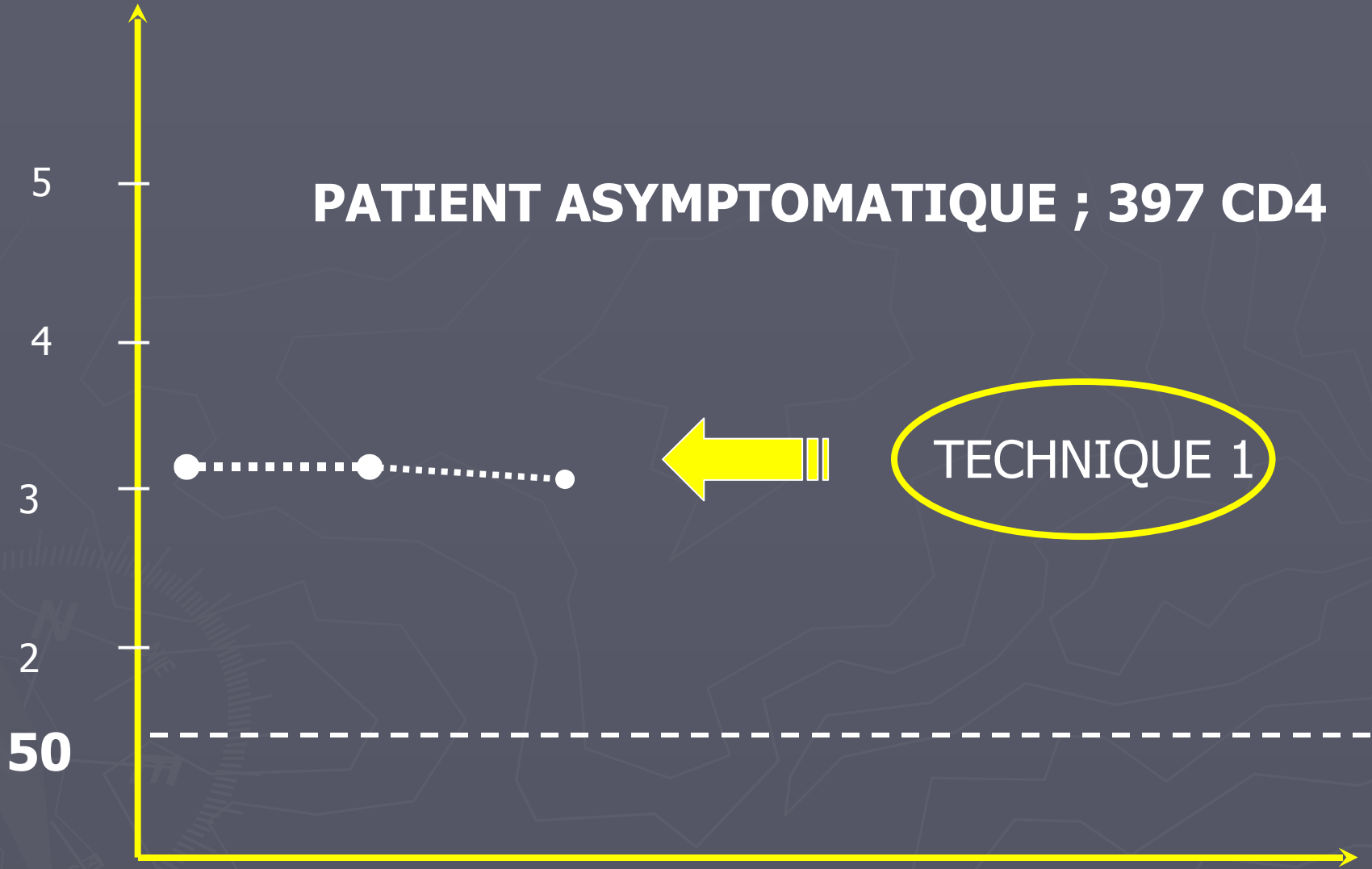
* CV (BL) : perte d'≈ **10%** CD4
(B.Rodrigues et al ; JAMA , Sept 2006)

* CV (BL) : **47%** SIDA et **50%** DECES vs 29/26 CD4
(J.W.Mellors et al ; JAMA , June 2007)

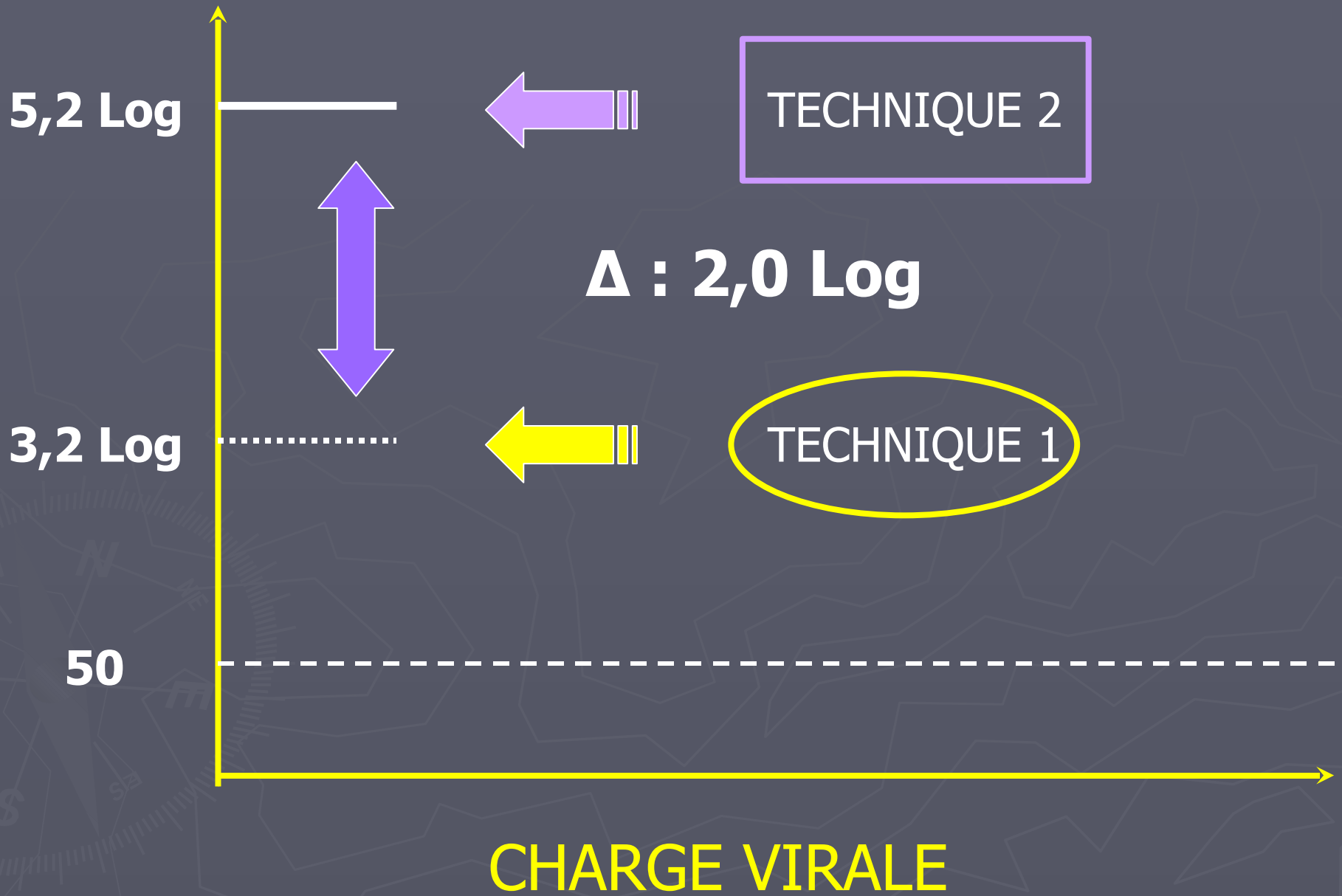
The prognostic strength of HIV-1 RNA is consistent with a central role of viral replication, manifest as viremia, in AIDS pathogenesis. It supports the use of HIV-1 RNA for estimating prognosis in untreated HIV-1 infection.

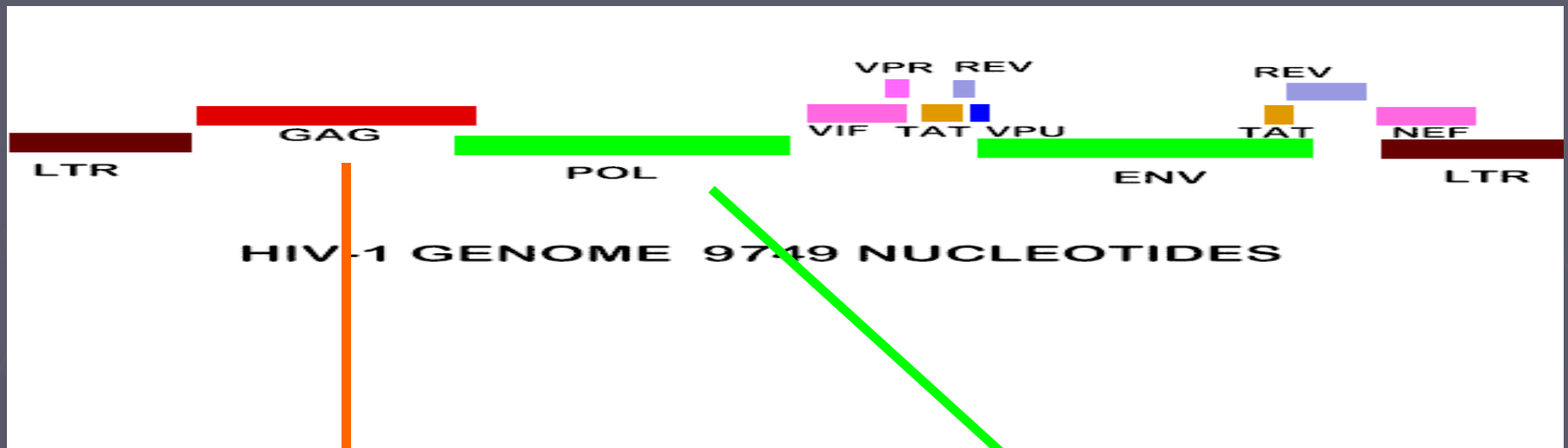
CV (Log)

PATIENT ASYMPTOMATIQUE ; 397 CD4



CHARGE VIRALE





• **ROCHE** (AMPLICOR , TAQMAN)
(Groupe M : A à H)

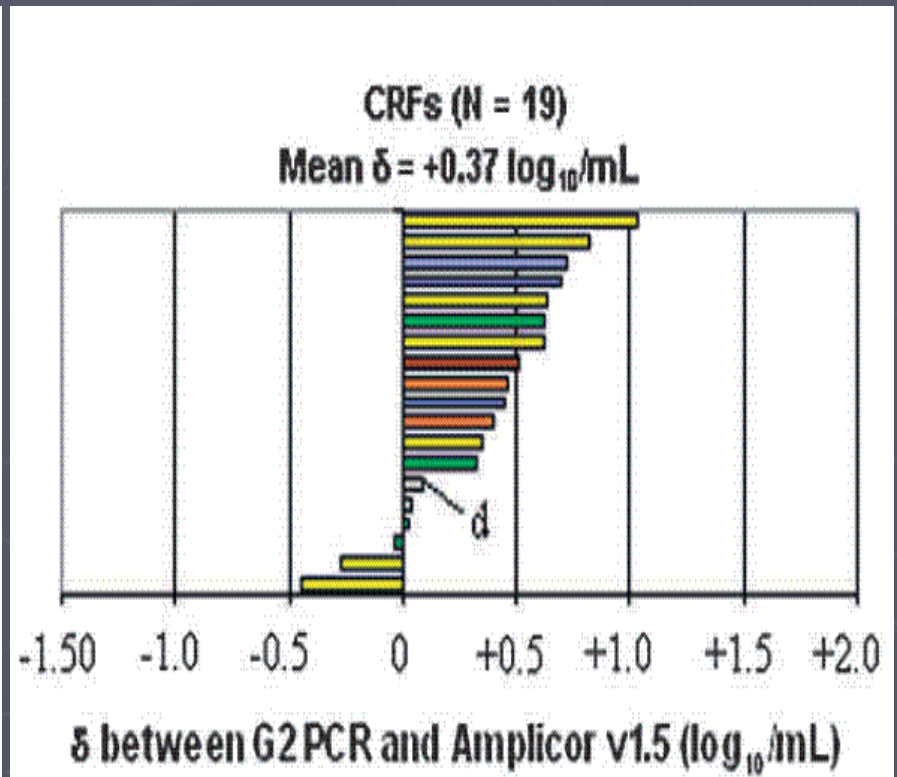
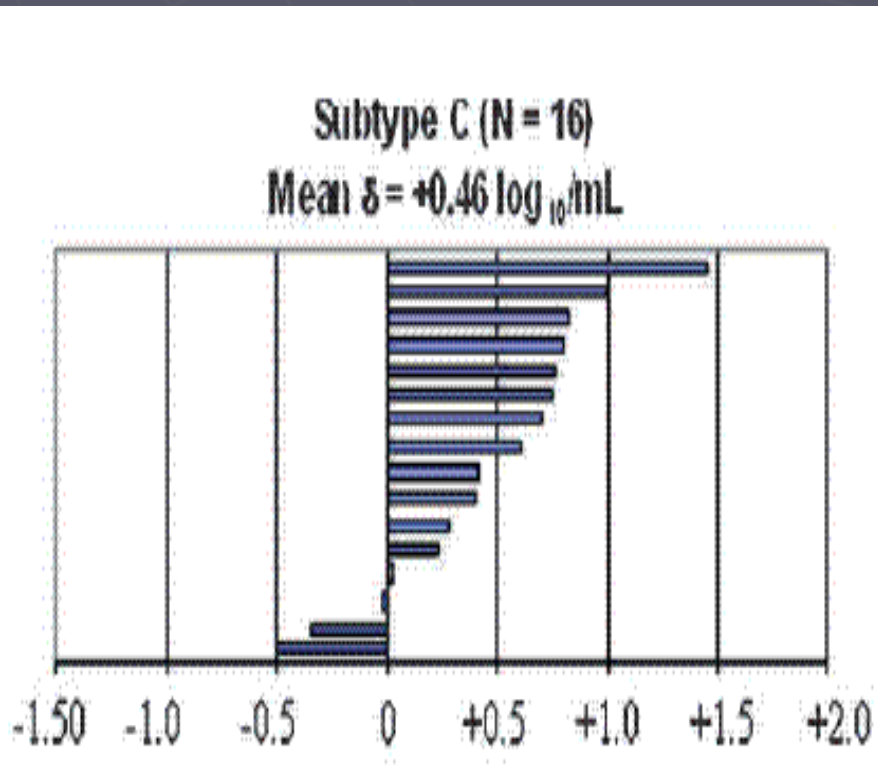
• **bioMérieux** (EASY Q)
(Groupe M et certains CRF)

• **BAYER** (VERSANT)
(Groupe M : A à G)

• **ABBOTT** (Real Time)
(Groupes M : A à G
et N , O)

IMPACT OF HIV-1 GENETIC DIVERSITY
ON PLASMA HIV-1 RNA QUANTIFICATION
F.ROUET et al ; J.AIDS in press

Sous quantification de **30%** des non-B et **14%** des B
(Amplicor) par rapport à ANRS G2 ($\Delta 0,51\log$)

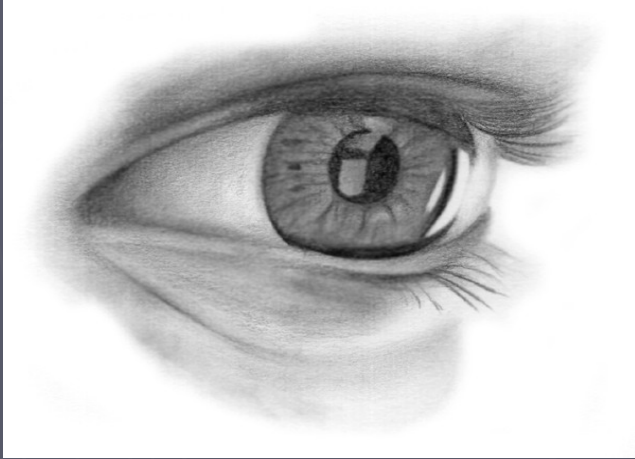


Effacité des IP's

KLEAN	FPV/r	LPV/r
<400	73	71
<50	66	65
CD4	+176	+191
Mut.PR	NON	NON

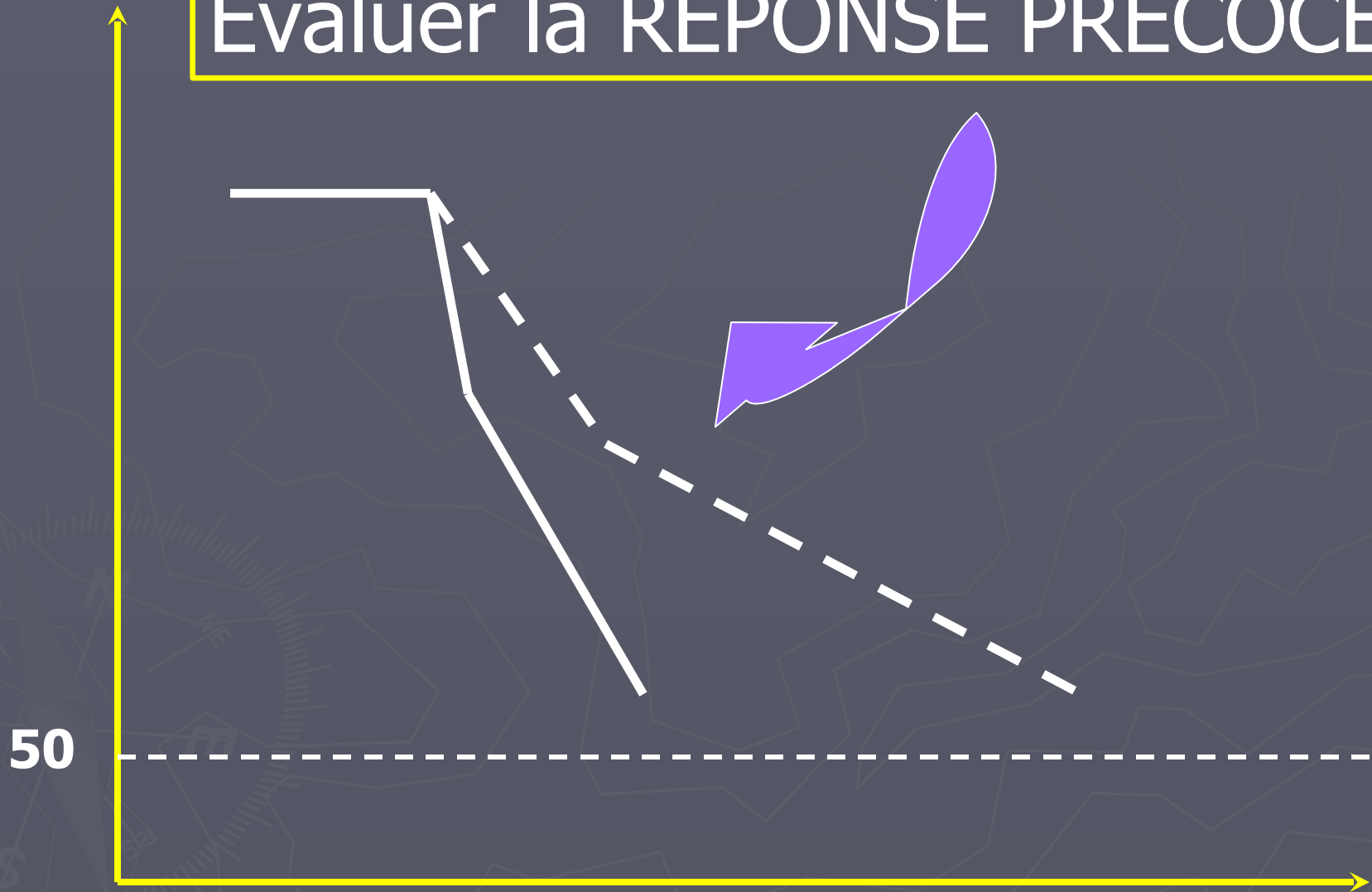
GEMINI	SQV/r	LPV/r
<400	81	84
<50	69	75
CD4	+157	+140
Mut.PR	NON	NON

Mise au point...



IL N'EXISTE PAS DE
RELATION
ENTRE LA « **BARRIERE
GENETIQUE** » d'un IP
(LPV n=8 ; FPV n=4;
SQV n=4)
et
LA **PUISSANCE ANTIVIRALE**
DE LA MOLECULE

Evaluer la REPONSE PRECOCE

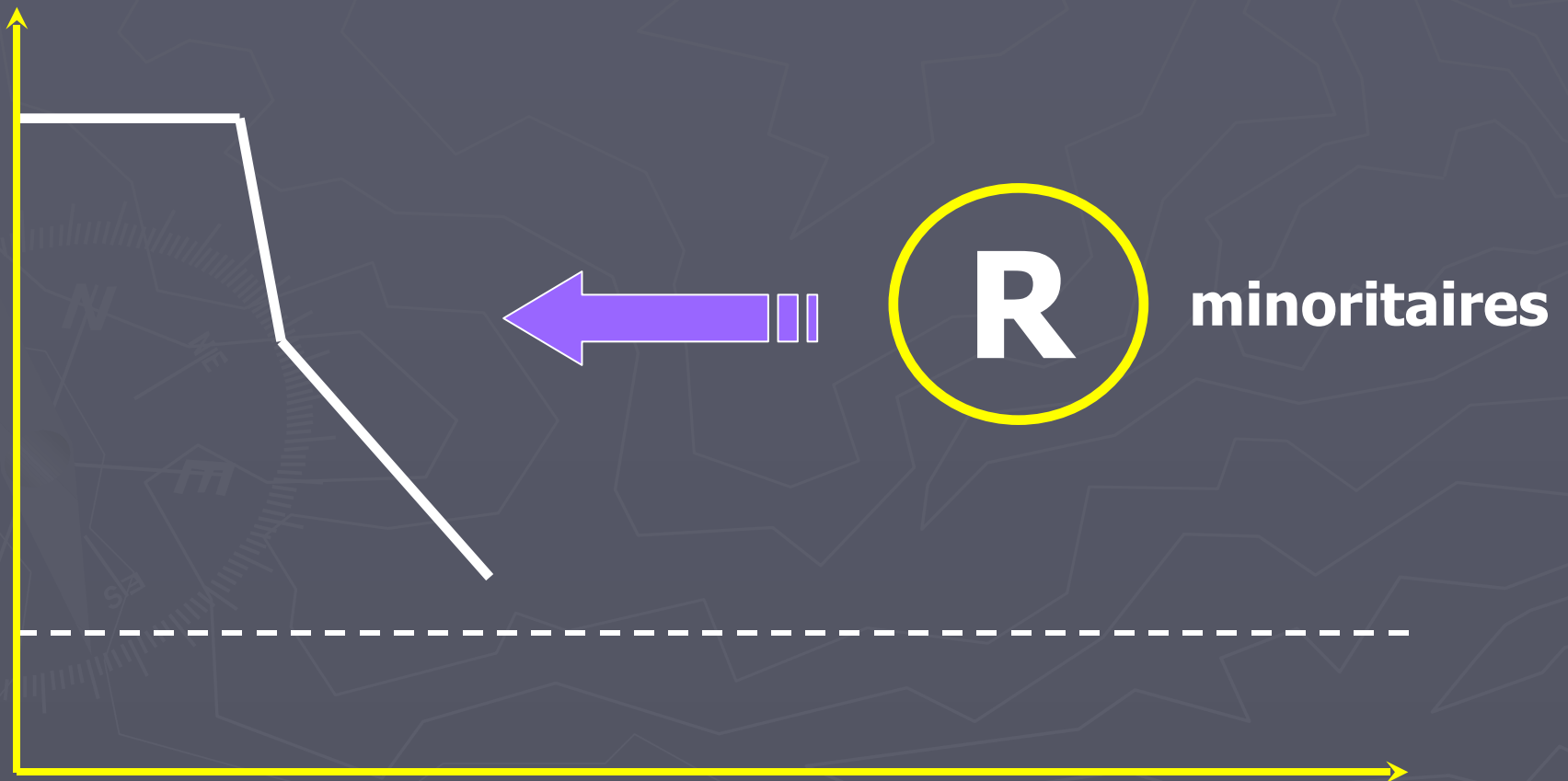


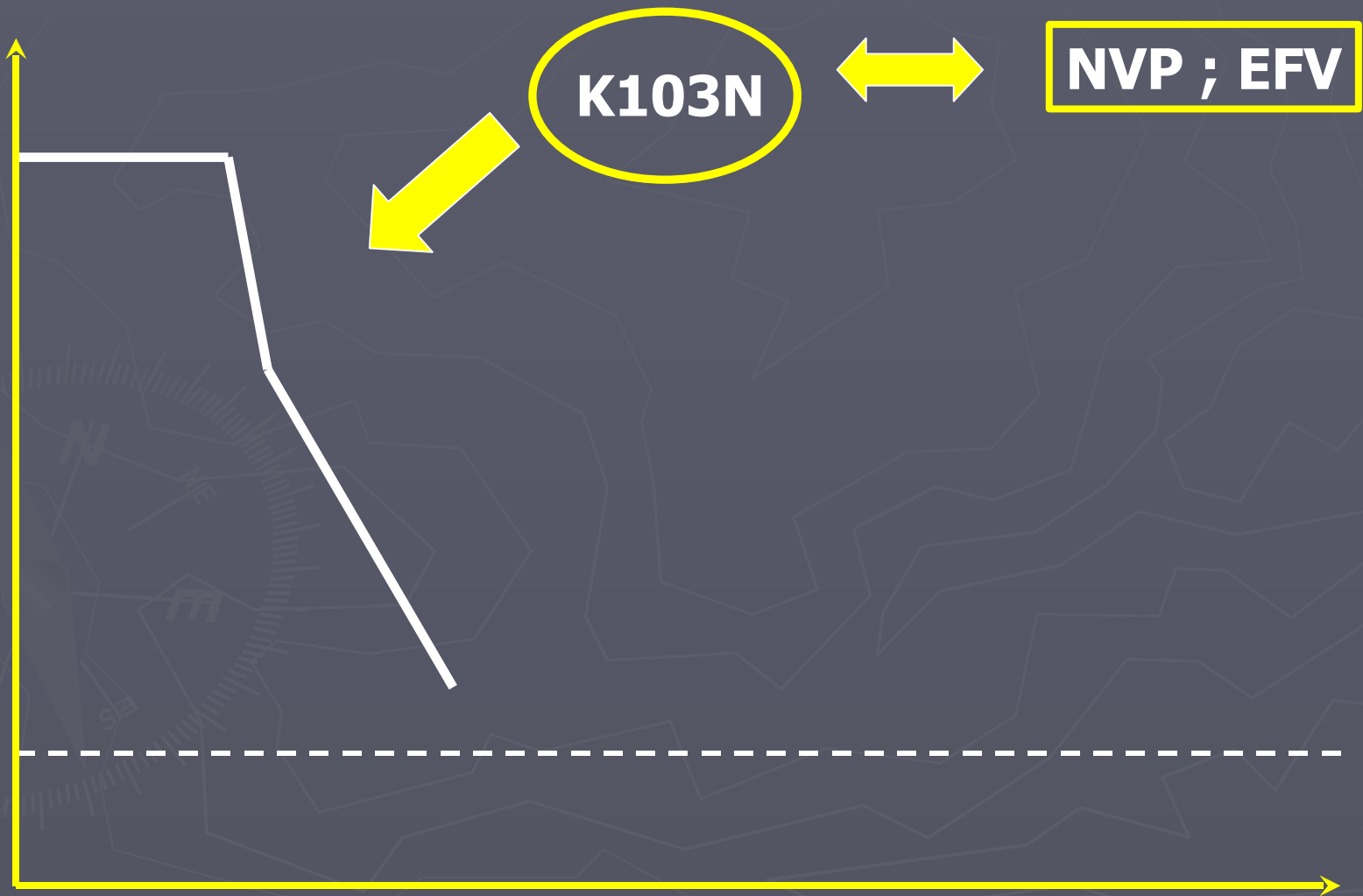
50

**RAPIDITE DE LA CHUTE DE LA CV PREDICTIVE
DE LA DURABILITE DE LA REPONSE VIROLOGIQUE**

RAPID SELECTION OF DRUG-RESISTANT HIV-1 DURING THE FIRST MONTHS OF SUPPRESSIVE ART IN TREATMENT-NAIVE PATIENTS

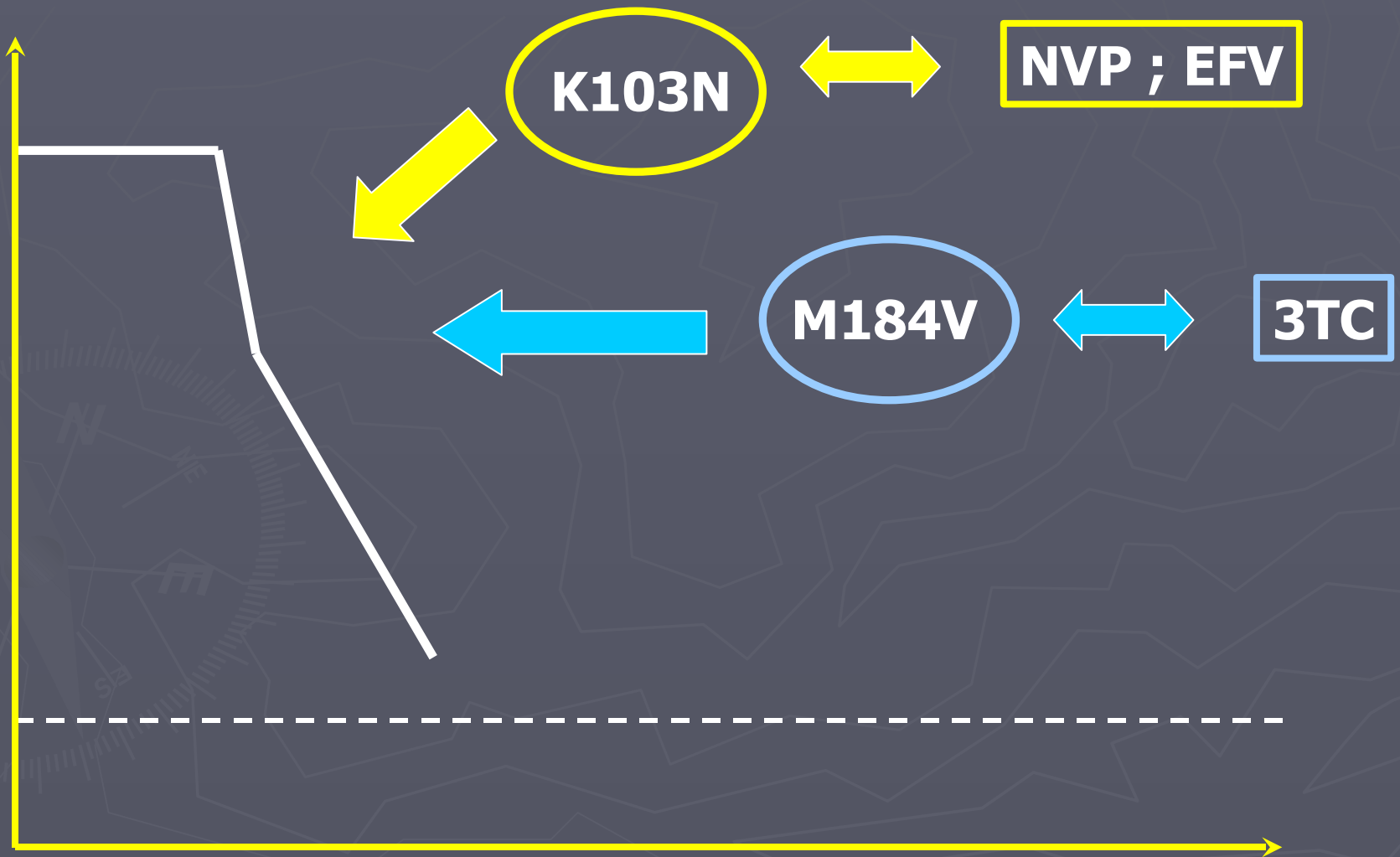
K.J.METZNER et al ; AIDS , 2007 , 21 , 703-711





K103N

NVP ; EFV

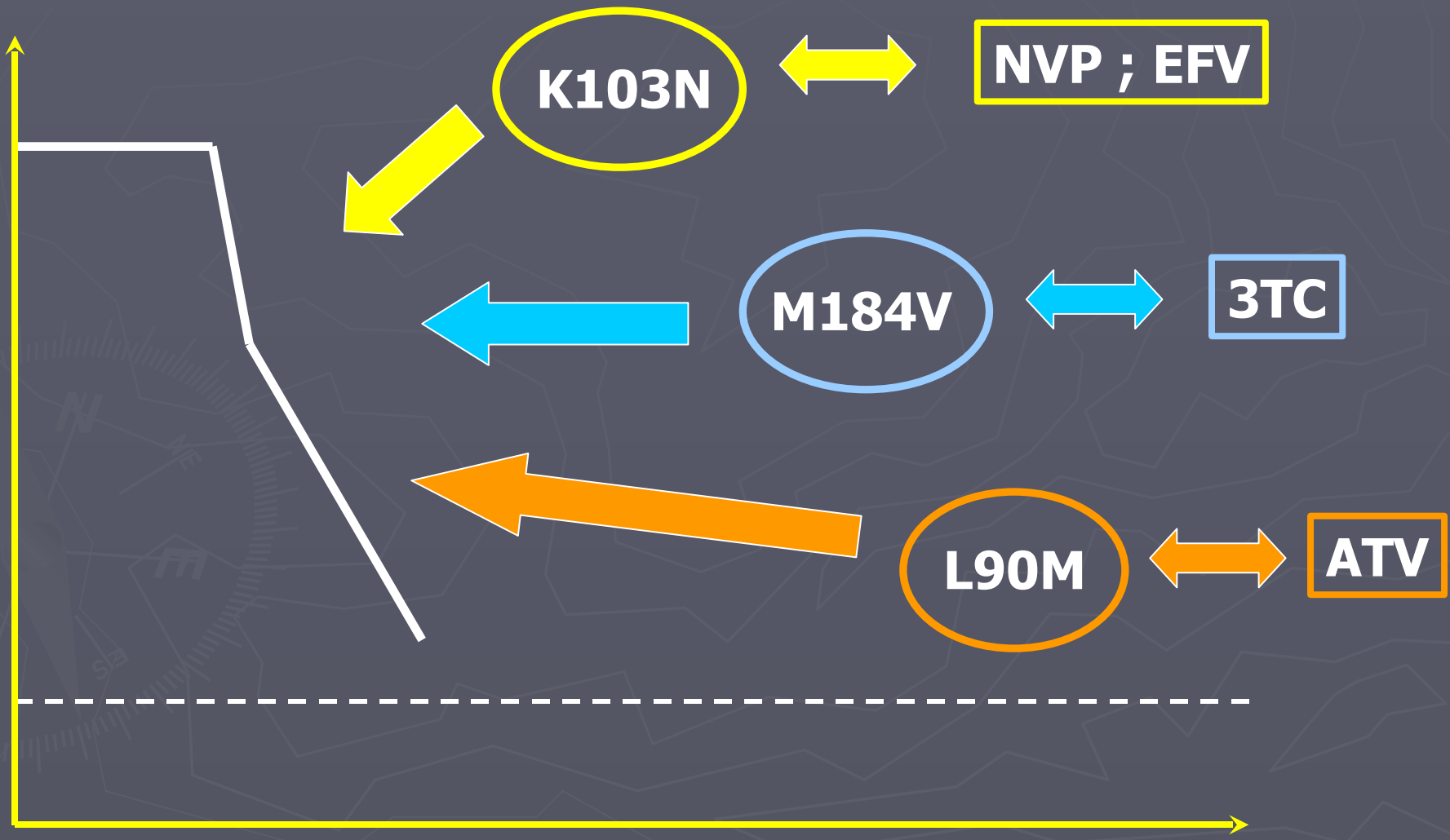


K103N

NVP ; EFV

M184V

3TC



K103N

NVP ; EFV

M184V

3TC

L90M

ATV

**RISQUE D' EMERGENCE DE RESISTANCE
PENDANT LA PHASE DE DECROISSANCE
DE LA CHARGE VIRALE**

**INDEPENDANT DE L'EXISTENCE
DE QUASI-ESPECES MUTEES AVANT
LE TRAITEMENT**



RISQUE D'EMERGENCE DE RESISTANCE

**INDEPENDANT DE L'EXISTENCE
DE QUASI-ESPECES MUTEES AVANT
LE TRAITEMENT**



RISQUE D'EMERGENCE DE RESISTANCE



**CORRELE AU DELAI
D'OBTENTION CV<50**

**INDEPENDANT DE L'EXISTENCE
DE QUASI-ESPECES MUTEES AVANT
LE TRAITEMENT**



RISQUE D'EMERGENCE DE RESISTANCE



**MOYEN DE LUTTE :
INTENSIFICATION**



**CORRELE AU DELAI
D'OBTENTION CV<50**

Determining the relative efficacy of highly active antiretroviral therapy

M.Louie et al ; JID ,2003,187,896-900

3 vs 2 CLASSES DIFFERENTES : Δ CV / JOUR

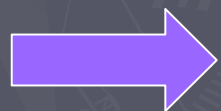
(2Nuc + 1NN + 1IP vs 2 Nuc + 1IP)

*** 0,52 vs 0,40 log (infection récente)**

*** 0,54 vs 0,37 log (infection chronique)**

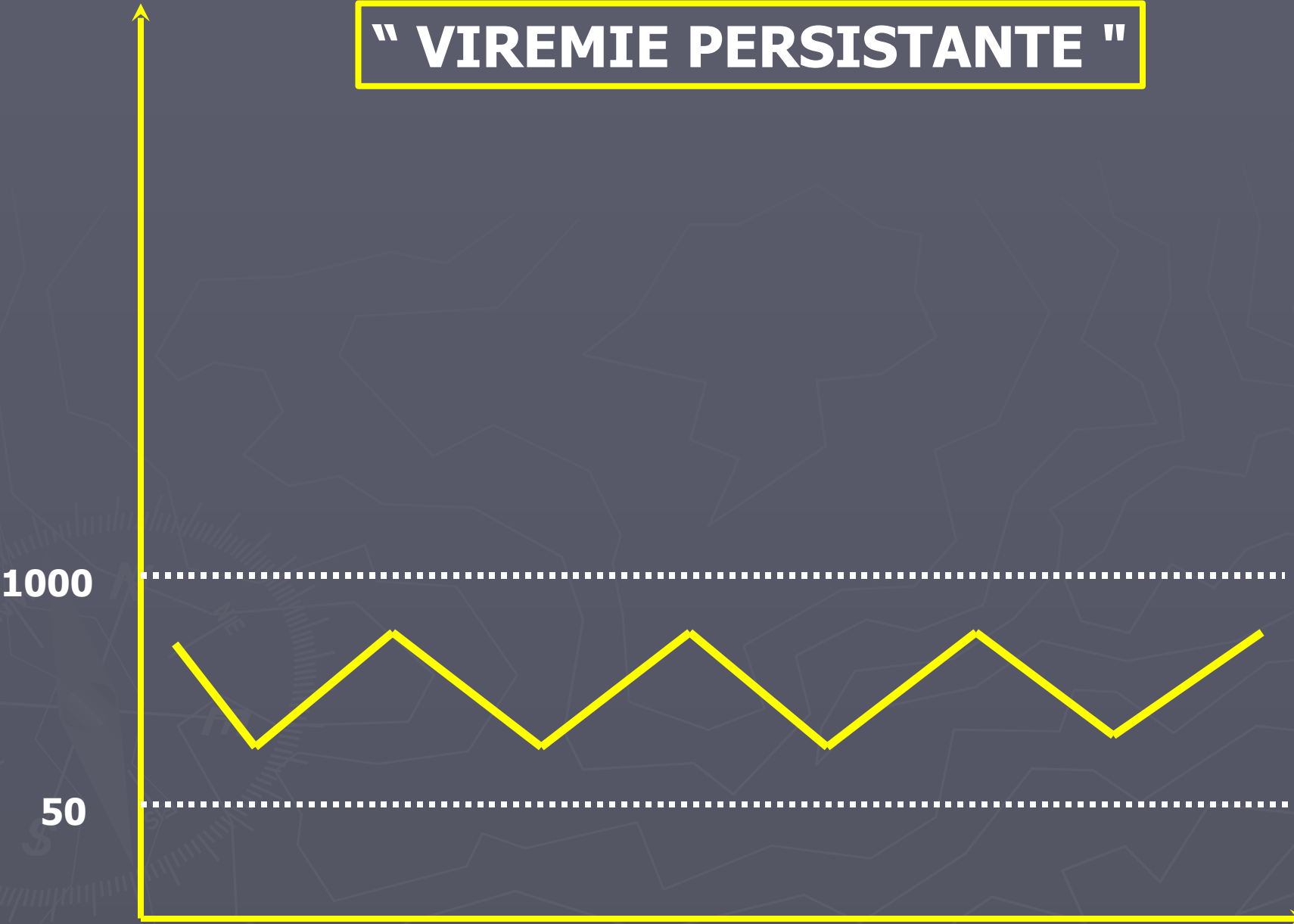
Increased antiretroviral potency by the addition of Enfuvirtide to a four-drug regimen in antiretroviral naive HIV-infected patients
J.Molto et al ; Antivir.Ther. 2006 ,11(1) ,47-51

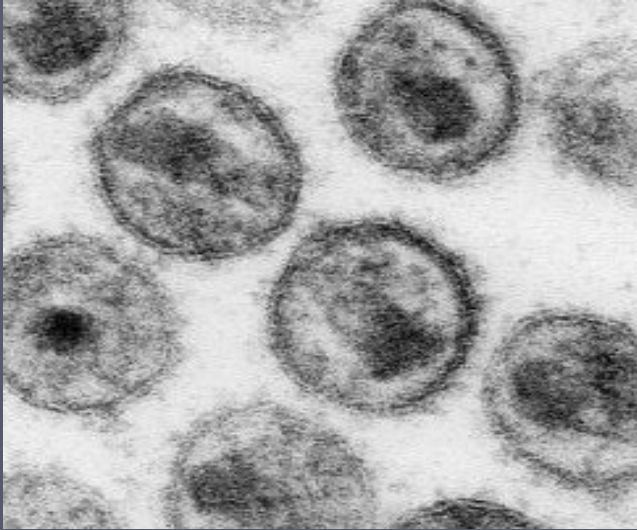
- ▶ TDF + 3TC + EFV + LPV/r ± ENF
- ▶ 8 Patients naifs / groupe
- ▶ CV / 6h (3j) ; CV / j (3-6j)

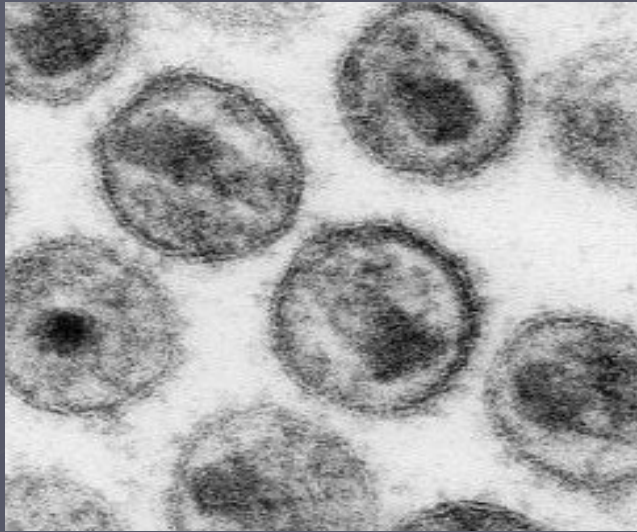


Chute CV/j : 0,80 vs 0,62 (p 0,045)

" VIREMIE PERSISTANTE "





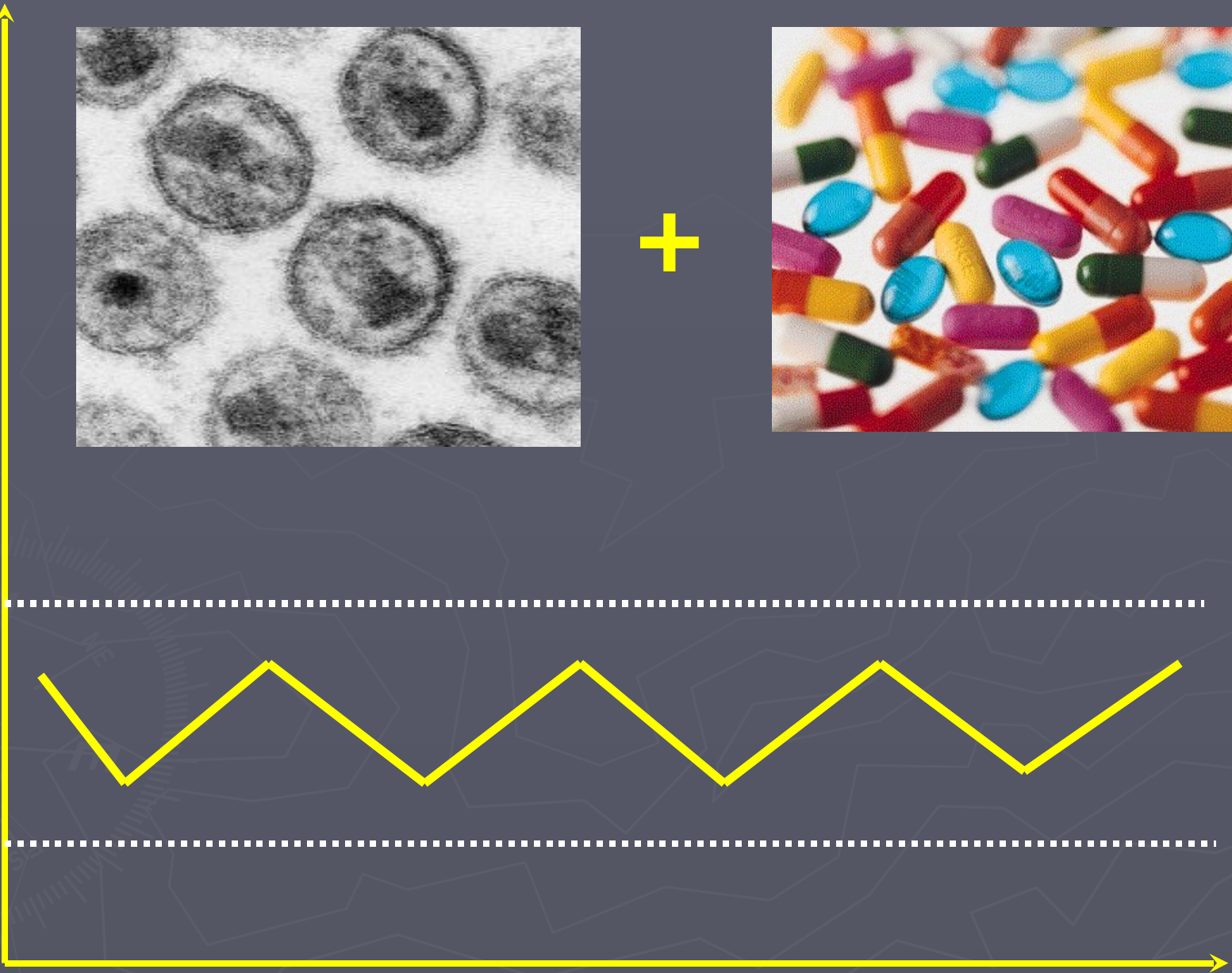


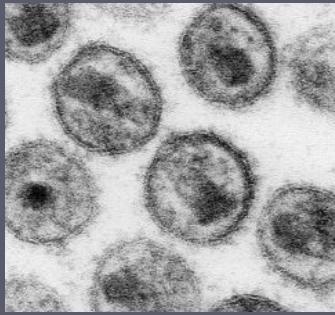
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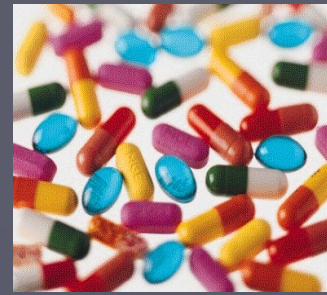
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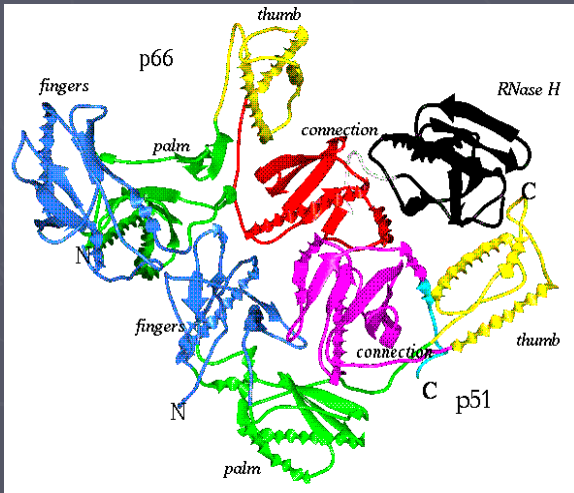




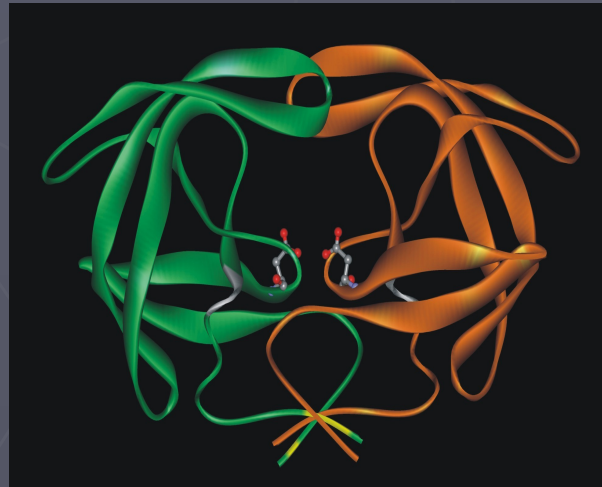
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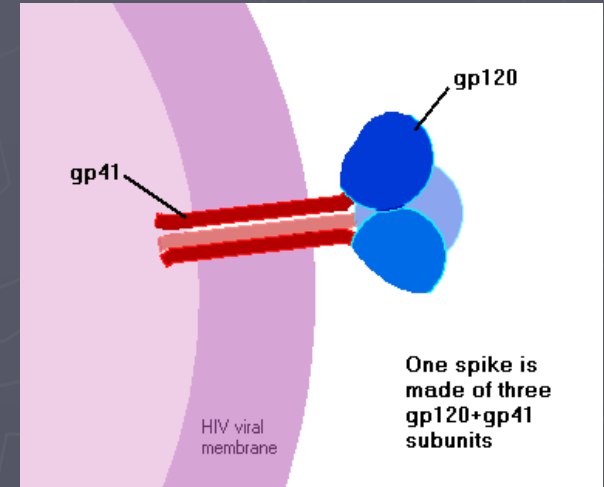
MUTATIONS



Nuc's
NonNuc's



IP



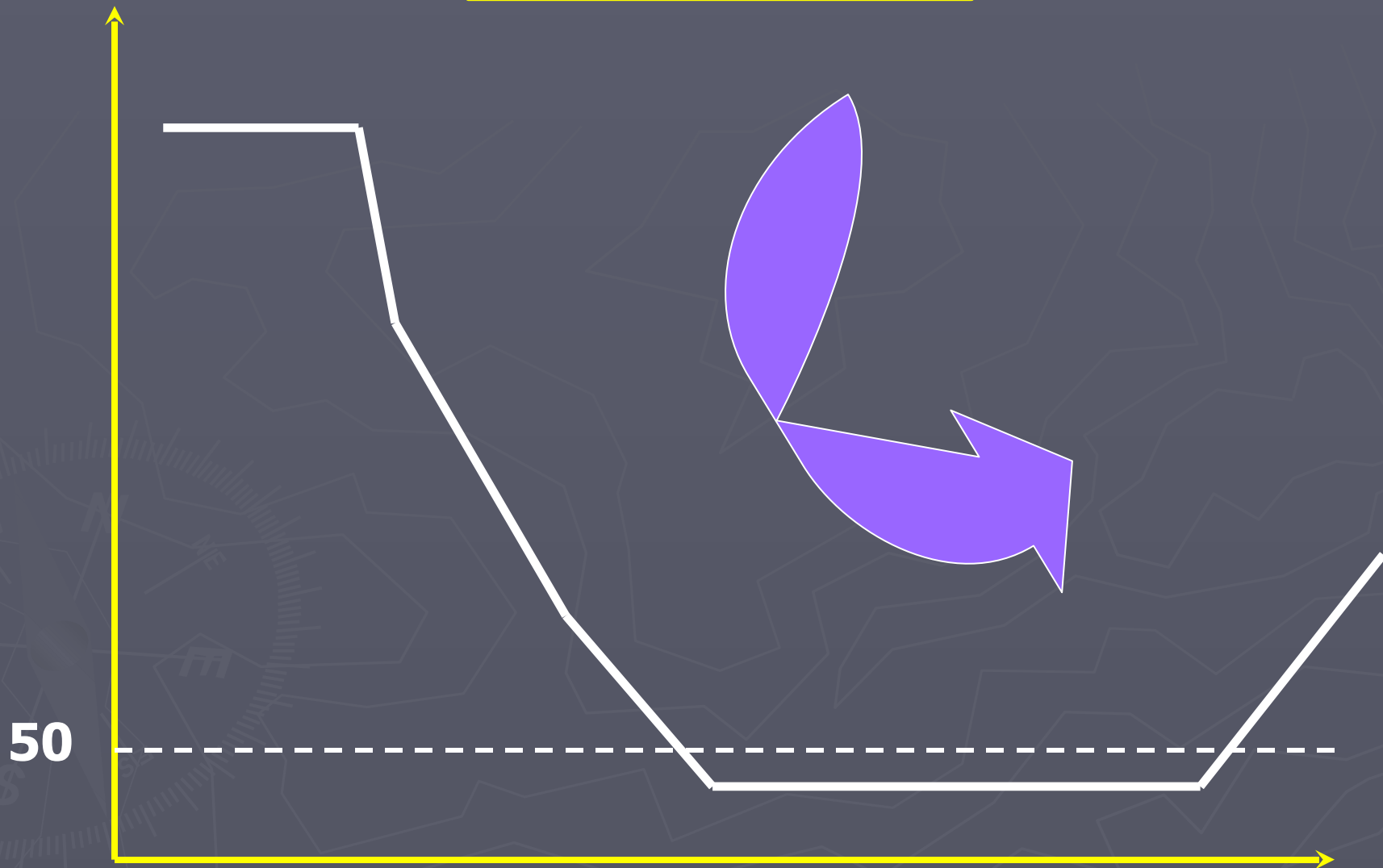
One spike is made of three gp120+gp41 subunits

"VIROC"
T20

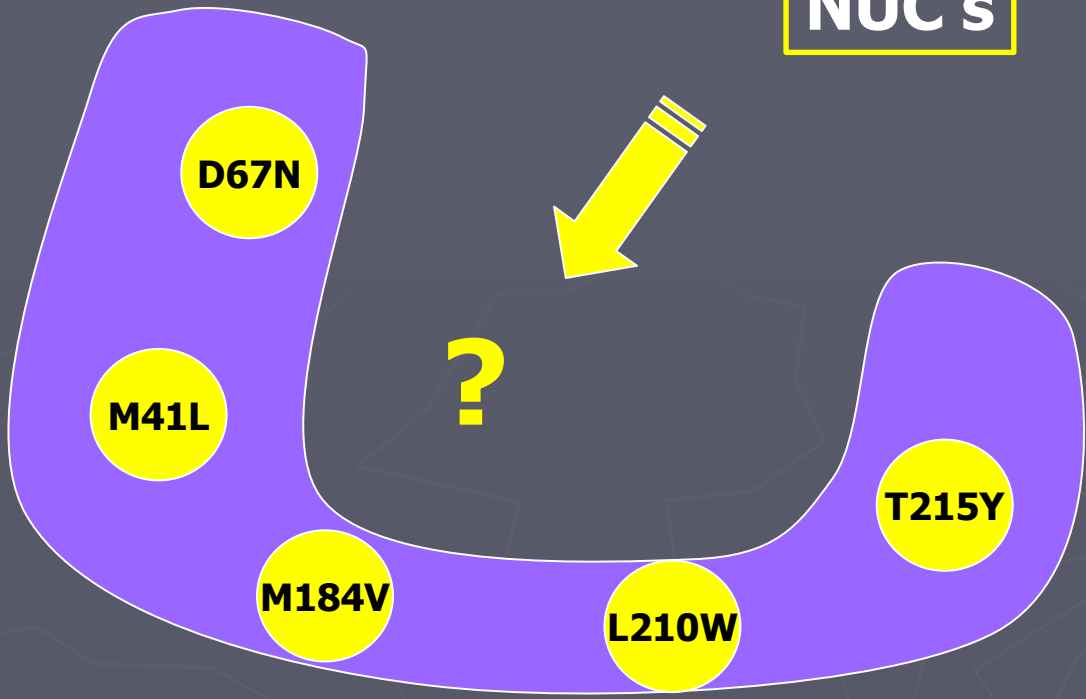
Evolution of drug resistance in HIV-infected patients remaining on a virologically failing combination antiretroviral therapy regimen
A.Cozzi-Lepri et al ; AIDS , 2007,21,721-32

- ▶ 110 Patients (EuroSIDA)
 - ▶ CV>400 (m:11 mois)
 - ▶ Traitement inchangé : 2"Géno" T0 et T6m
- * Acquisition de 2 mutations IAS
 - * Perte de 1,25 molécule ARV (Rega)

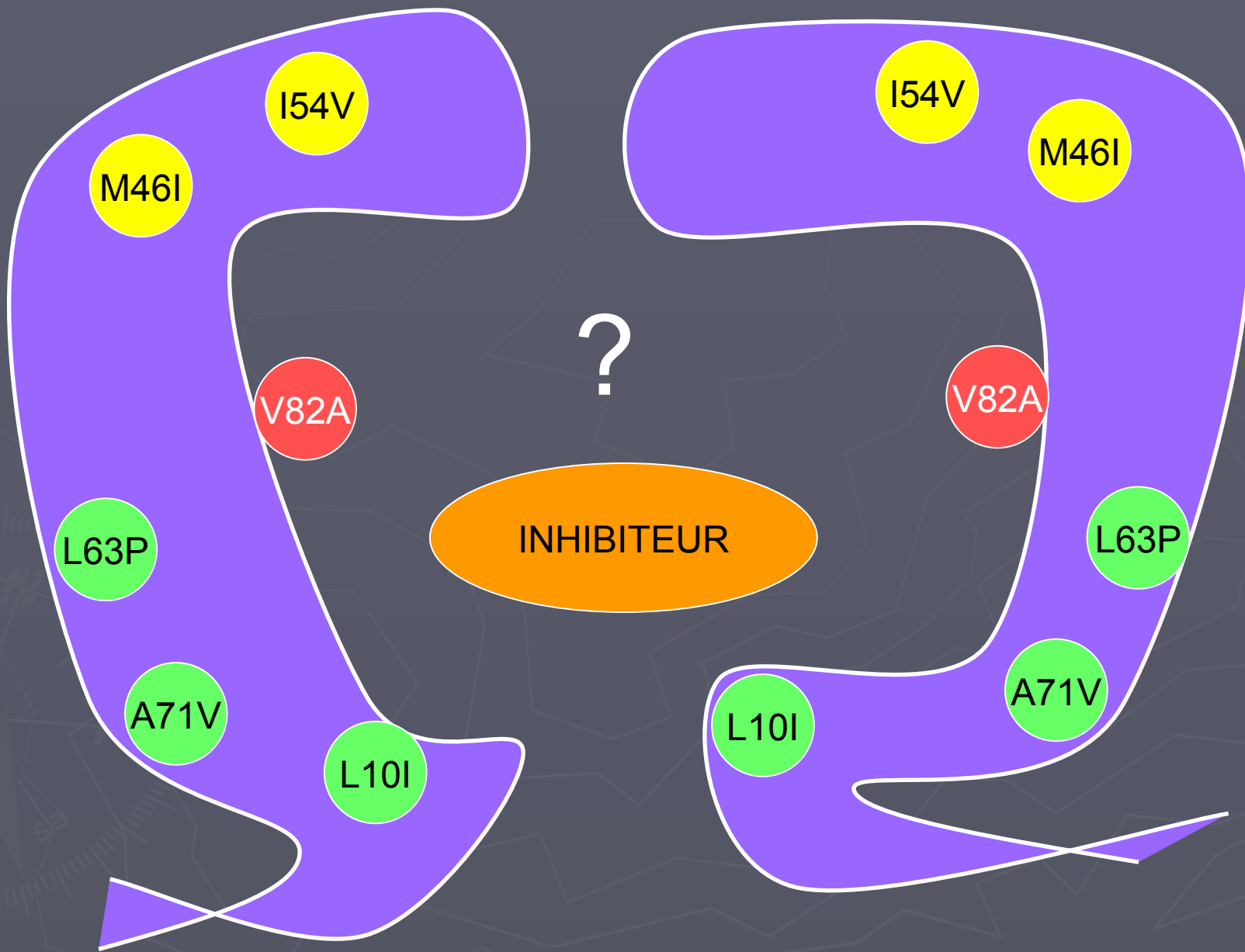
LORS D'UN ECHEC







NUC's



	3TC	ABC	AZT	D4T	DDI	FTC	TDF
ANRS	R	R	R	R	S	R	RP
HIV.DB	H	H	H	H	I	H	I

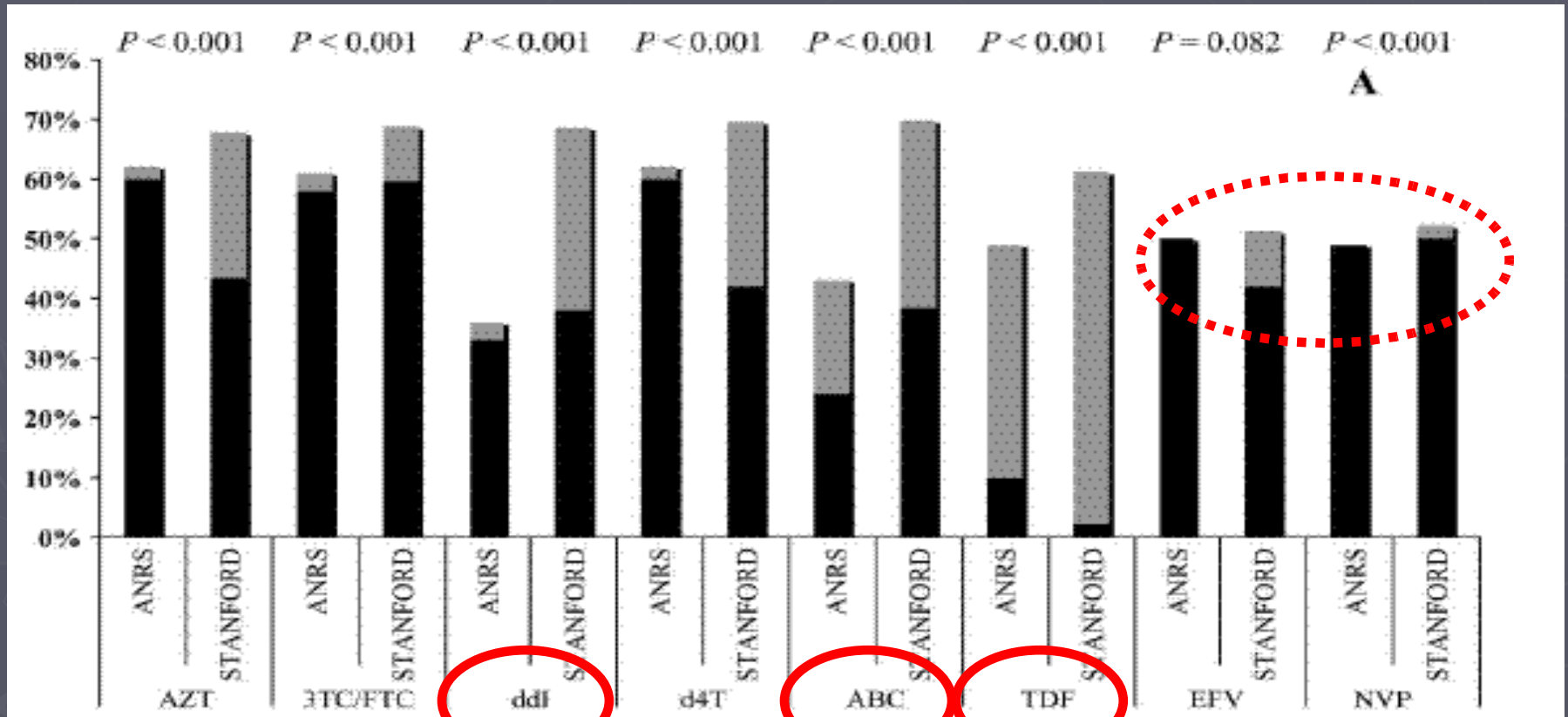


	IDV	SQV	NFV	f.APV	LPV	ATV	TPV	DRV
ANRS	R	RP	RP	S 	RP	S 	S 	S 
HIV DB	H 67	I 37	H 82	I 39	I 51	I 47	I 35	L 24

Prevalence of HIV-1 drug resistance in treated patients

A French Nationwide Study

D. Costagliola et al ; J.AIDS 2007 (in press)

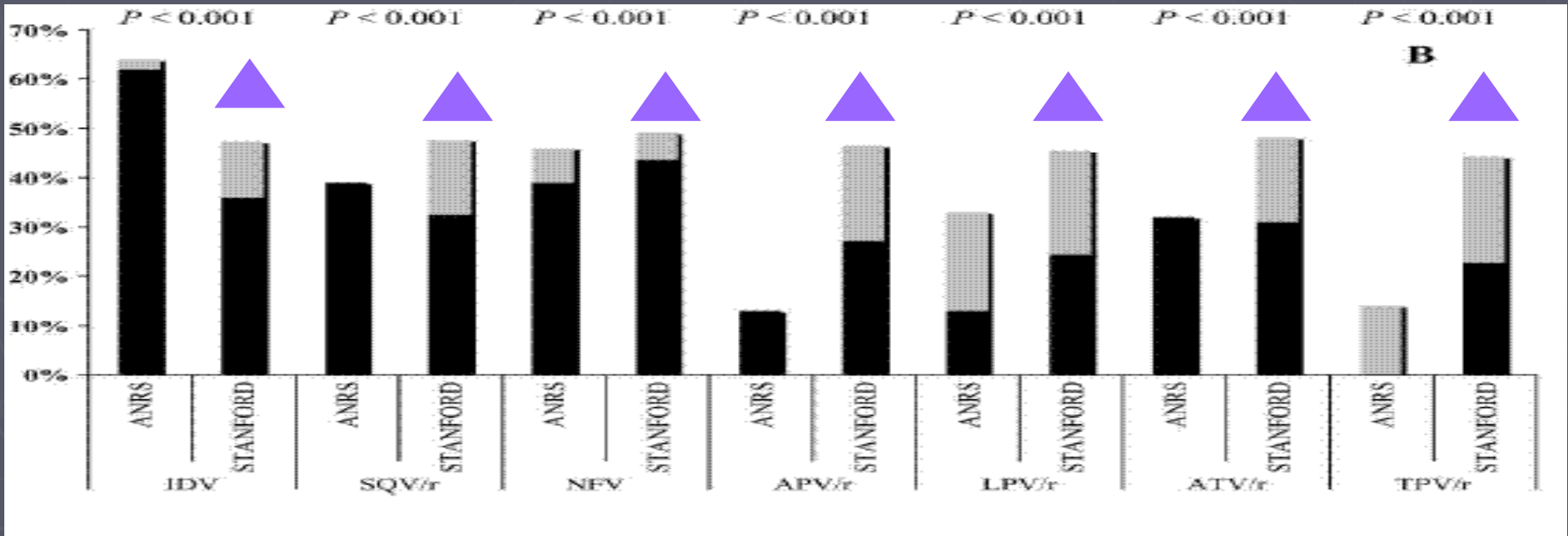


NN : OK ; ddI , ABC , TDF : ???

Prevalence of HIV-1 drug resistance in treated patients

A French Nationwide Study

D.Costagliola et al ; J.AIDS 2007 (in press)



ANRS : IDV >60% ; NFV , SQV , ATV 30-40% ; LPV , fAPV , TPV 10-15%

STANFORD : FREQUENCES SIMILAIRES DE RESISTANCE

Estimated potency of six different boosted protease inhibitors regimens in antiretroviral-experienced HIV patients. Impact of baseline protease resistance mutations

G.Ramirez-Olivencia et al ; 5th EHDRW Portugal
March 28-30 , 2007

- ▶ 422 patients " switchés " pour échec sous IP
- ▶ 162 LPV , 100 SQV , 59 ATV , 58 TPV ,
35 APV , 8 IDV
Chute CV > 1 log ou < 50

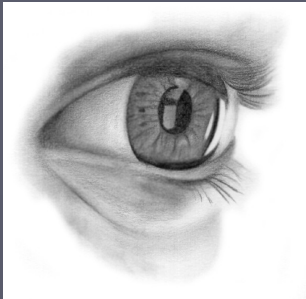
PAS DE DIFFERENCE SIGNIFICATIVE ENTRE LES IP'S EN TERME DE SUCCES VIROLOGIQUE

3 MARQUEURS PREDICTIFS DE REPONSE

1. Chaque mutation supplémentaire diminue les chances de succes d' $\approx 30\%$ ($p < 0.001$)

2. Chaque mutation préexistante diminue les chances de succes d' $\approx 40\%$ ($p < 0.001$)

3. L'utilisation d'ENF. augmente Les chances de succes d' ≈ 10 fois ($p < 0.001$)



MISE AU POINT...

* « FAUX NEGATIF »

* CHOIX DU BACKBONE ASSOCIE AUX NOUVELLES MOLECULES

* RESIST , POWER , BENCHMRK , TMC 125

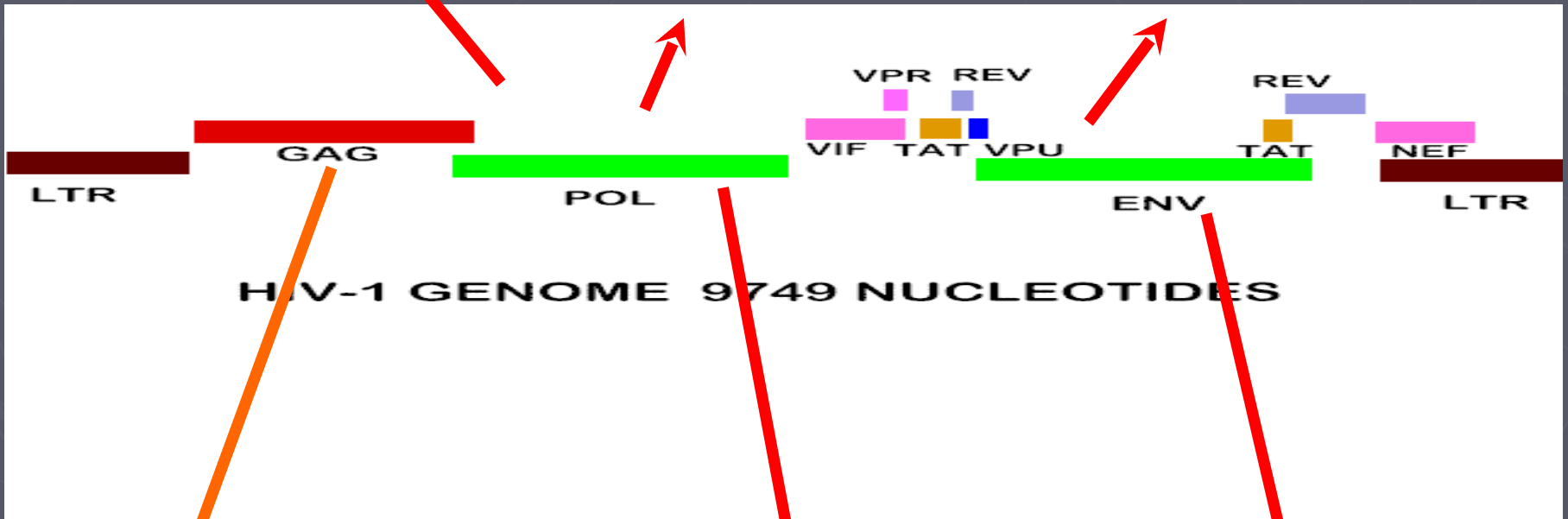


FUZEON

PR : Nvx
"Algos"

RT : autres
régions

Gp 41 : HR2



Sites de
clivage

INT : à faire

Gp 120 : à faire

CONCLUSION

