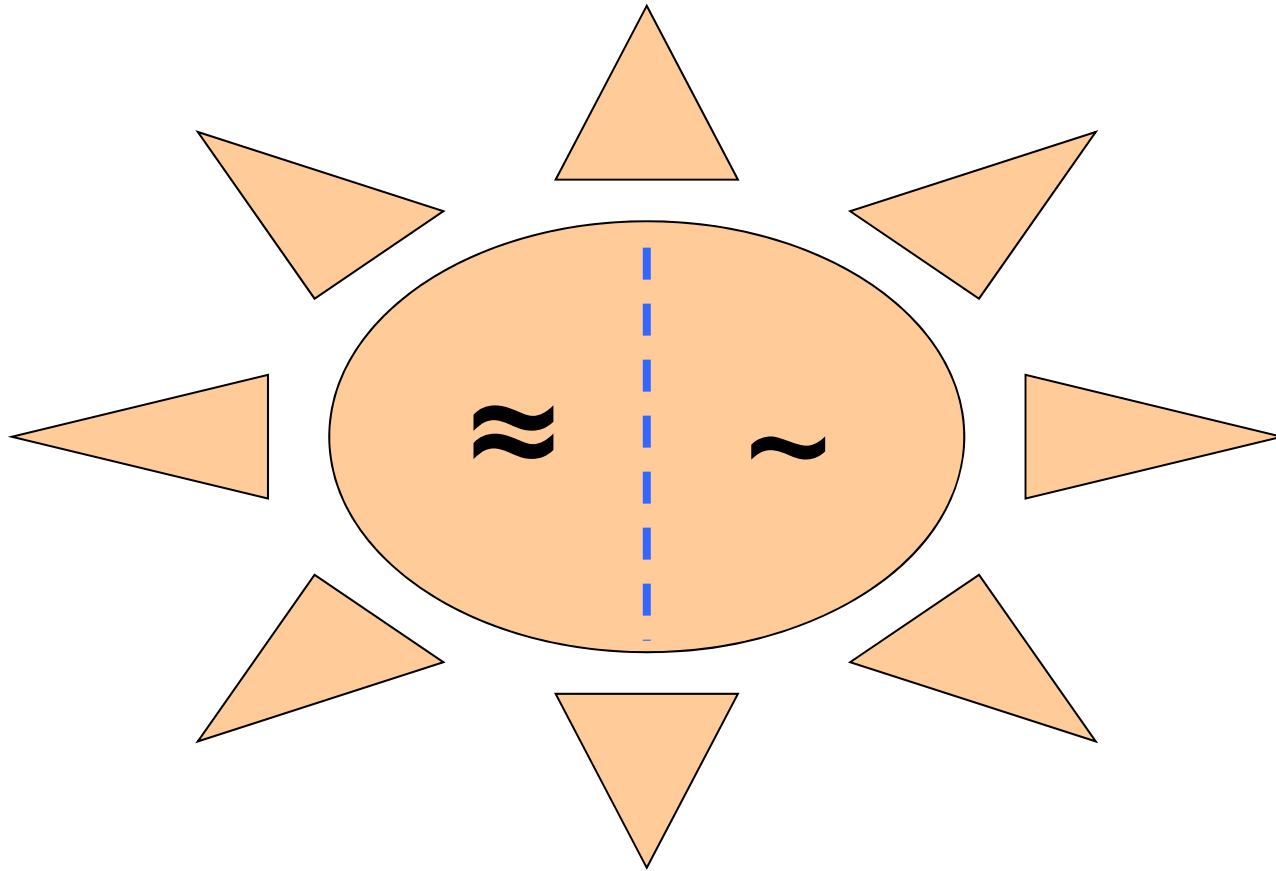


Les Antirétroviraux Mécanismes d'action et Résistance

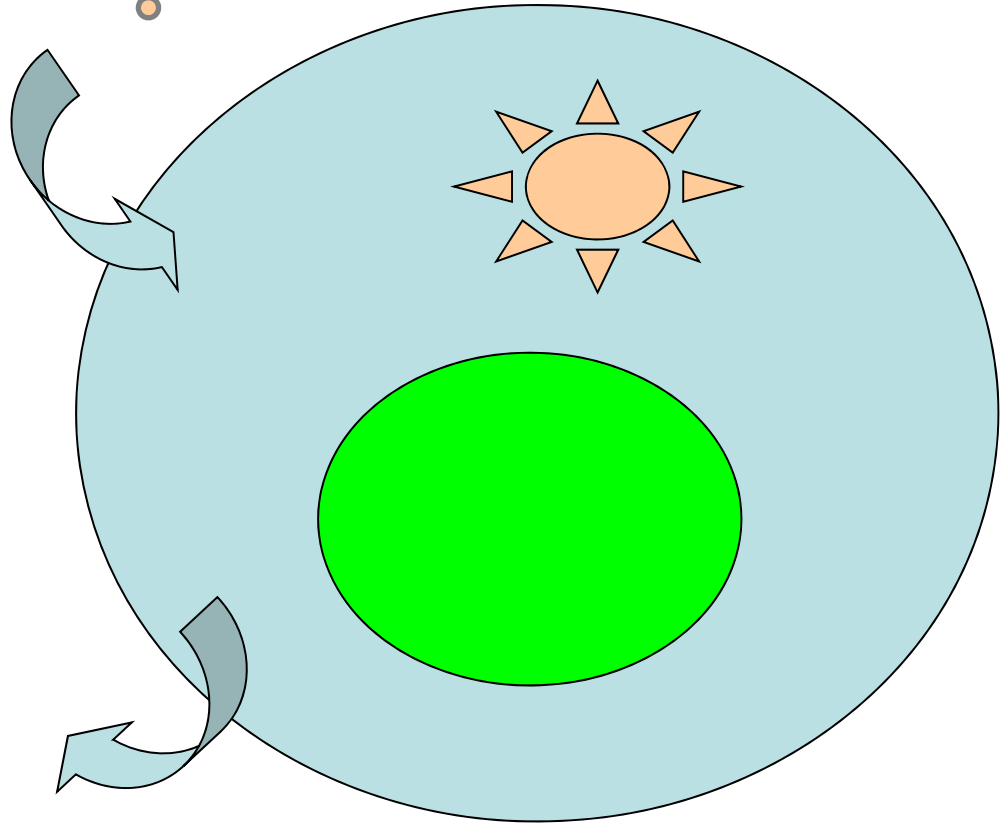
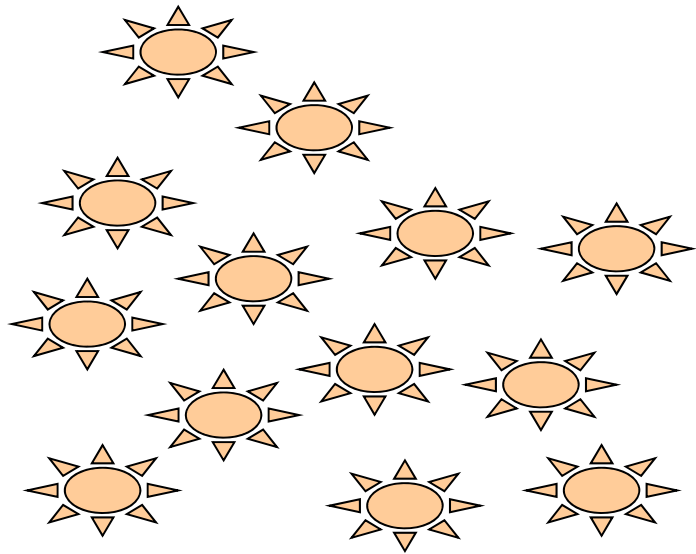
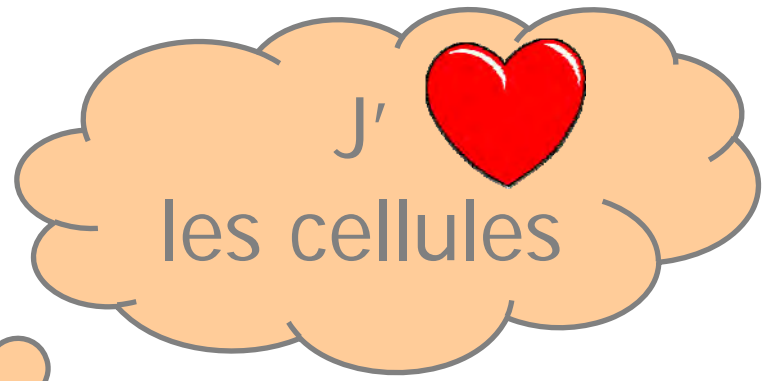
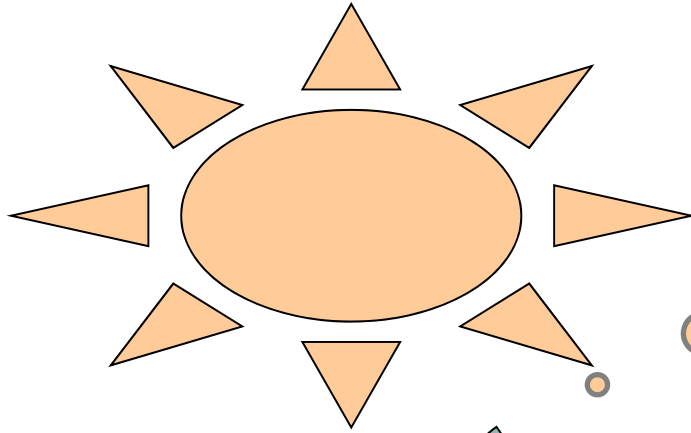
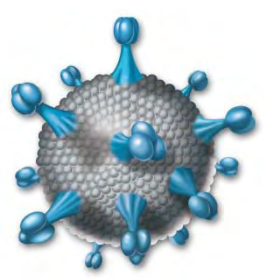
D.U Infectiologie ; 08 Mars 2011

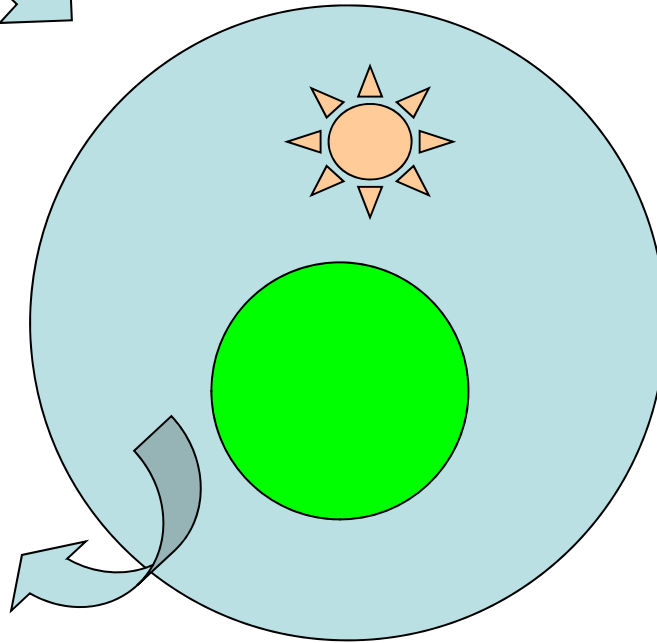
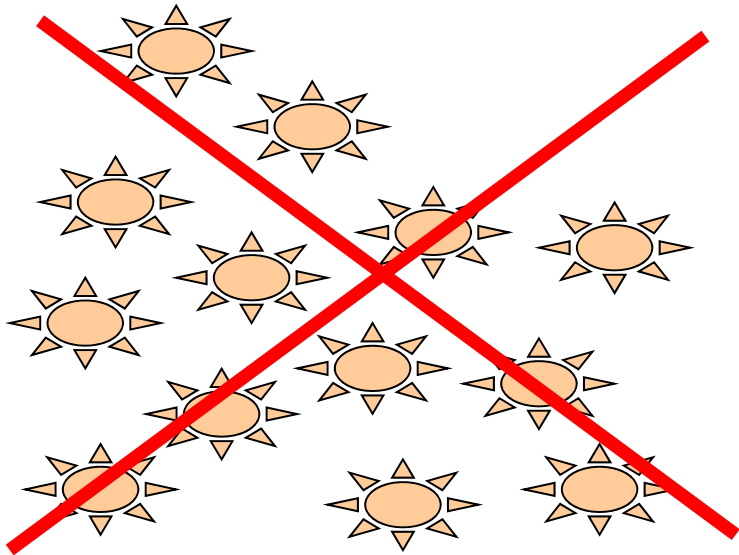
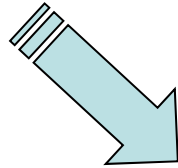
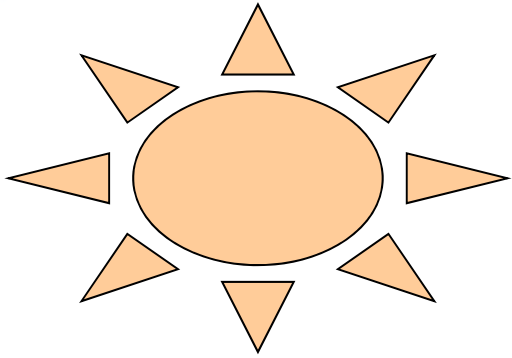
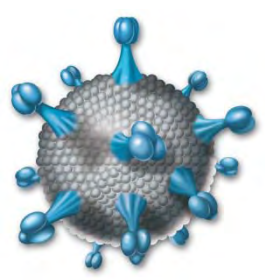
JC TARDY

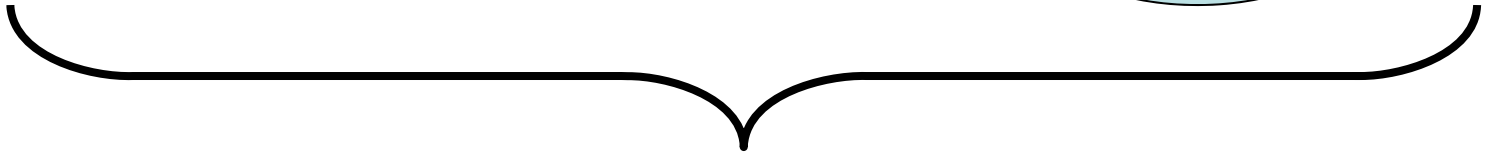
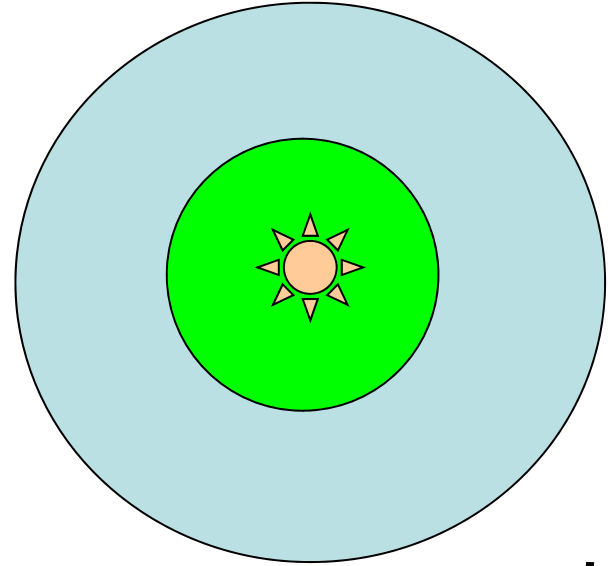
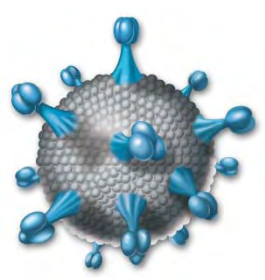


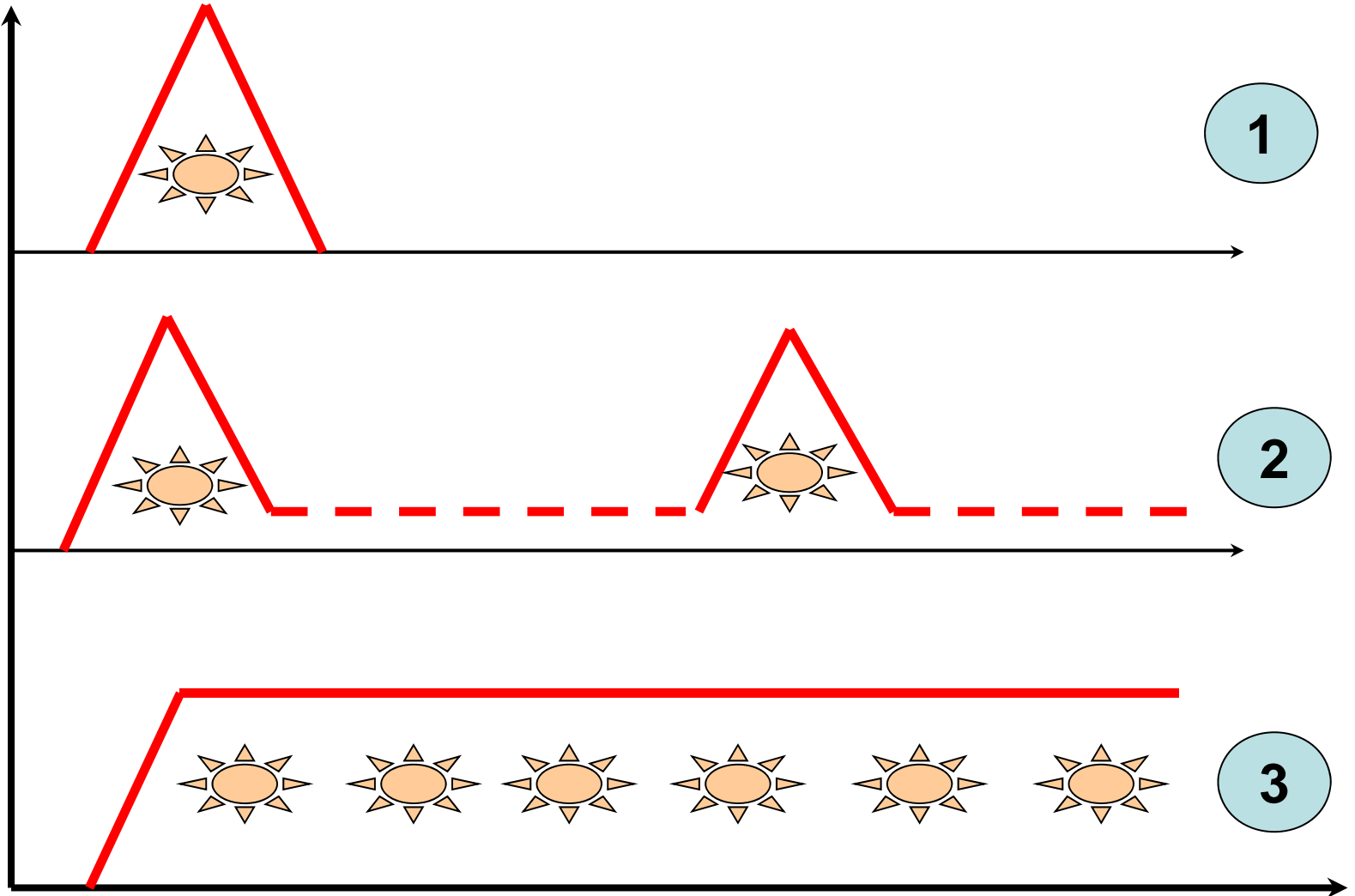
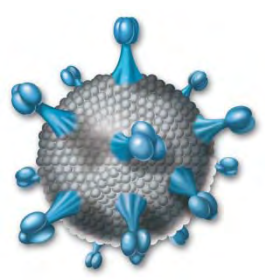
C'est en 1953 que André Lwoff a énoncé les trois caractères fondamentaux faisant des virus des entités originales :

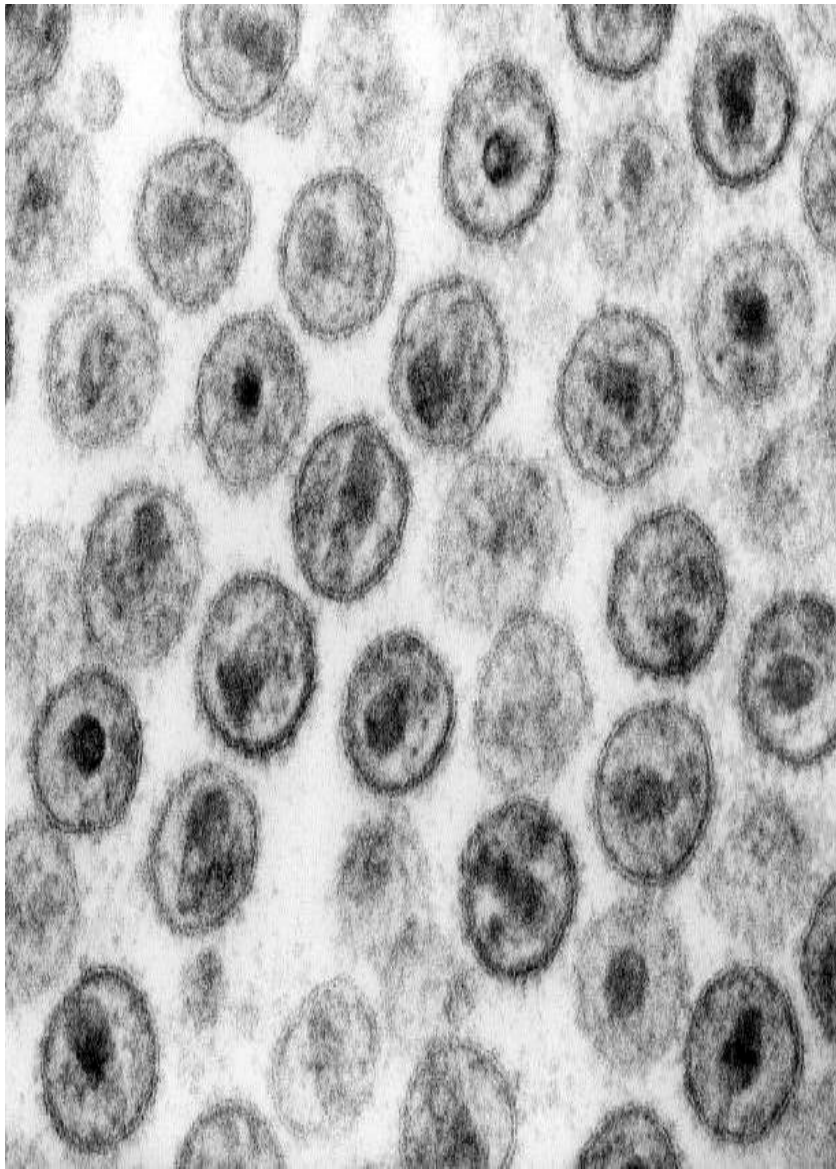
- 1/ les virus ne contiennent qu'un seul type d'acide nucléique (ADN ou ARN) qui constitue le génome viral.
- 2/ les virus se reproduisent à partir de leur matériel génétique et par réplication.
- 3/ les virus sont doués de parasitisme intracellulaire absolu.

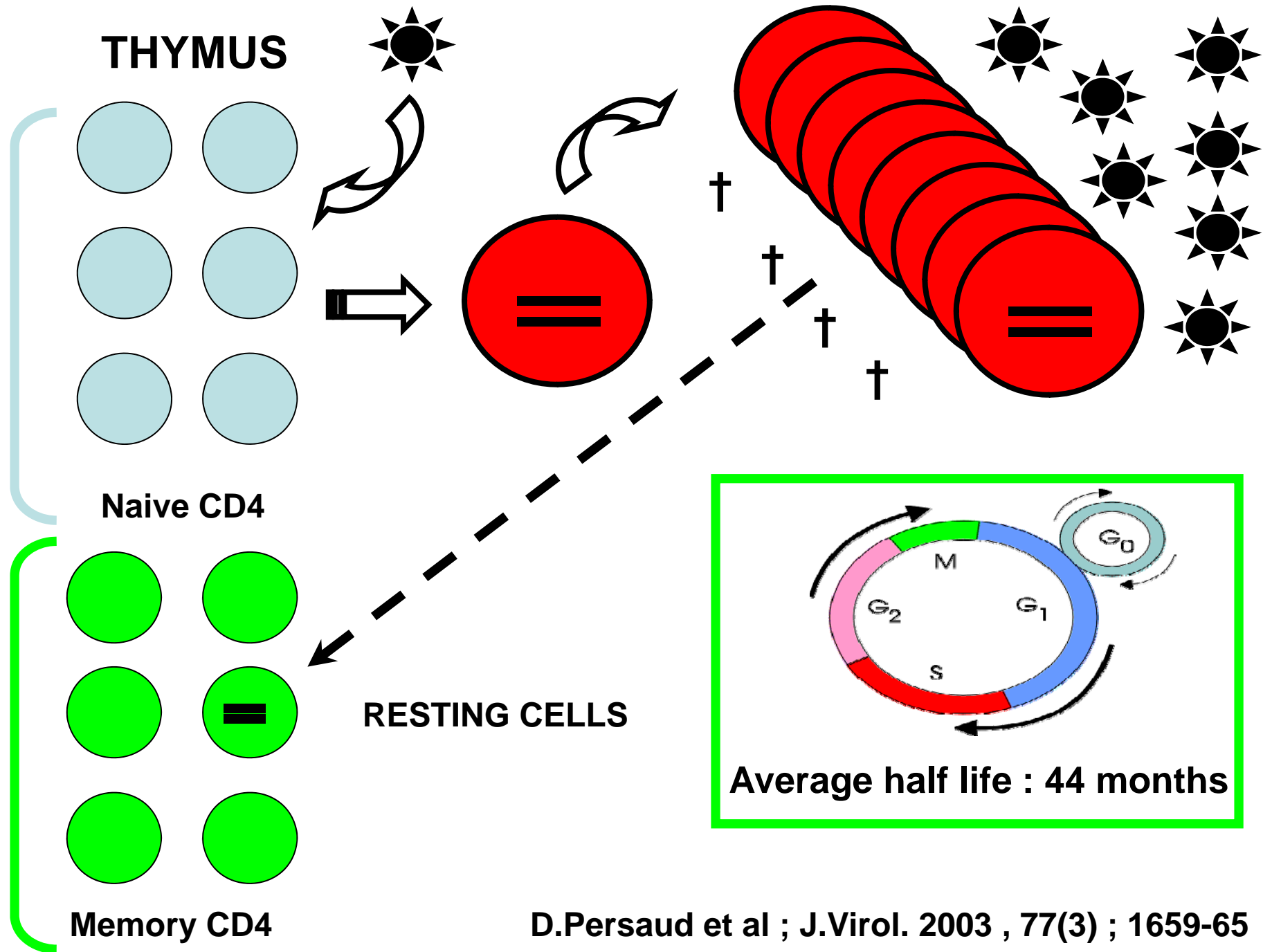




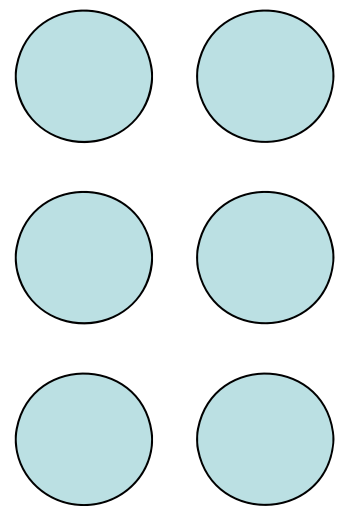




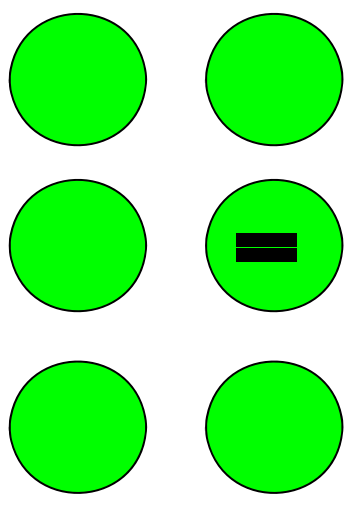




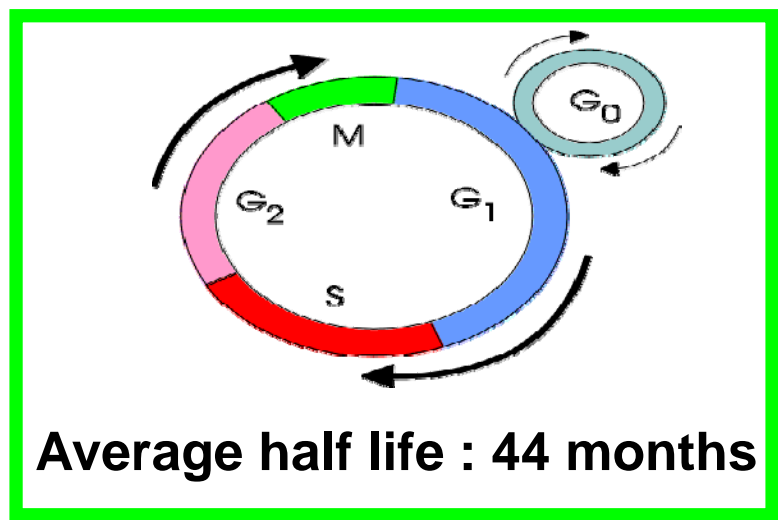
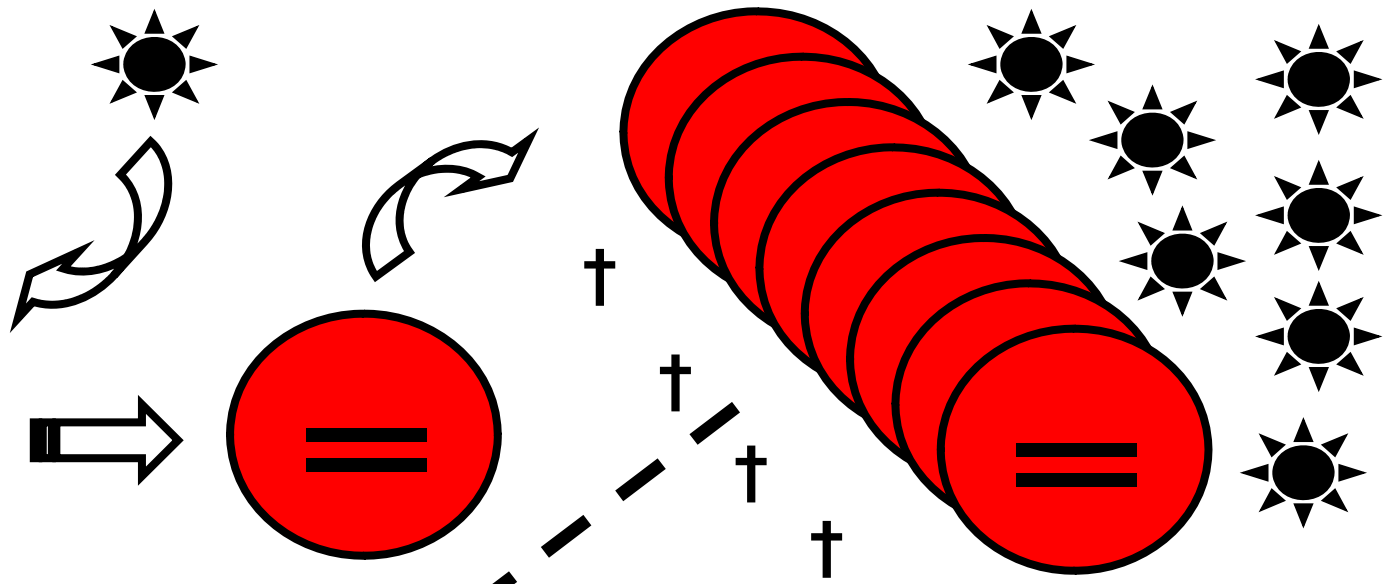
THYMUS



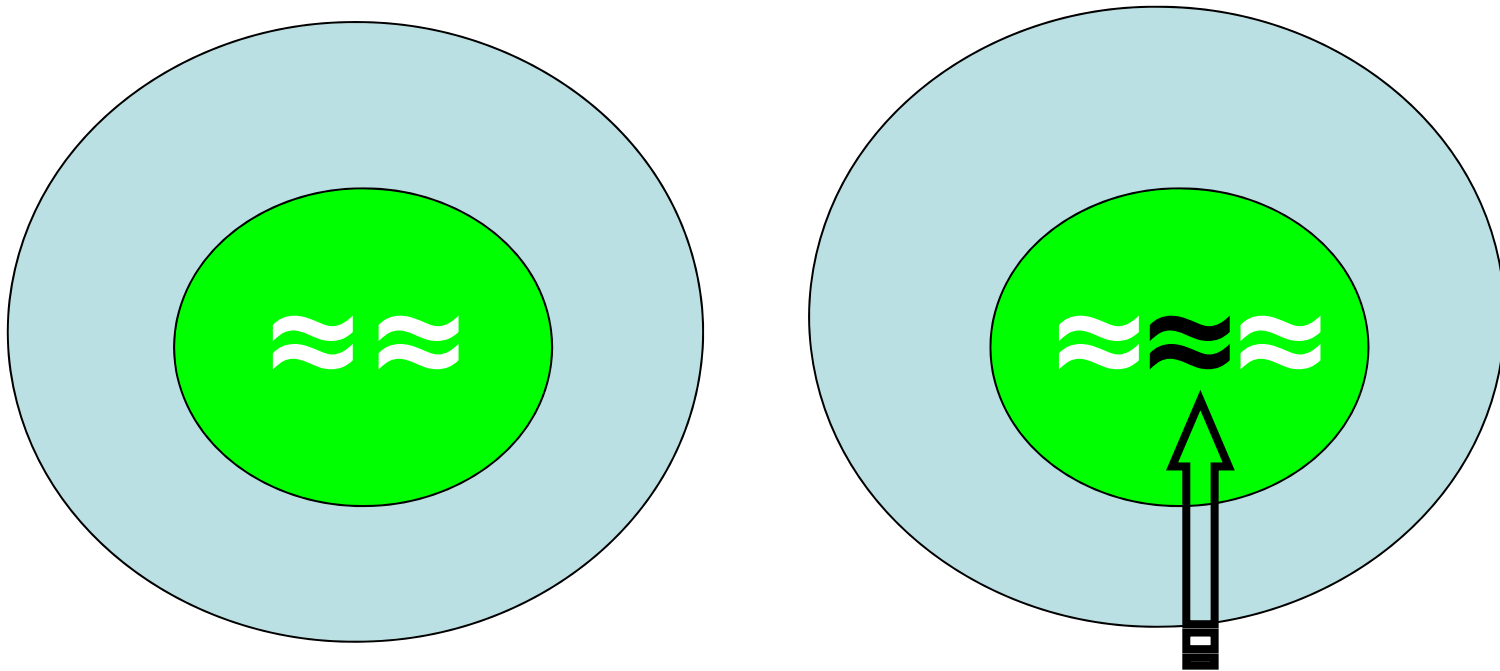
Naive CD4



Memory CD4

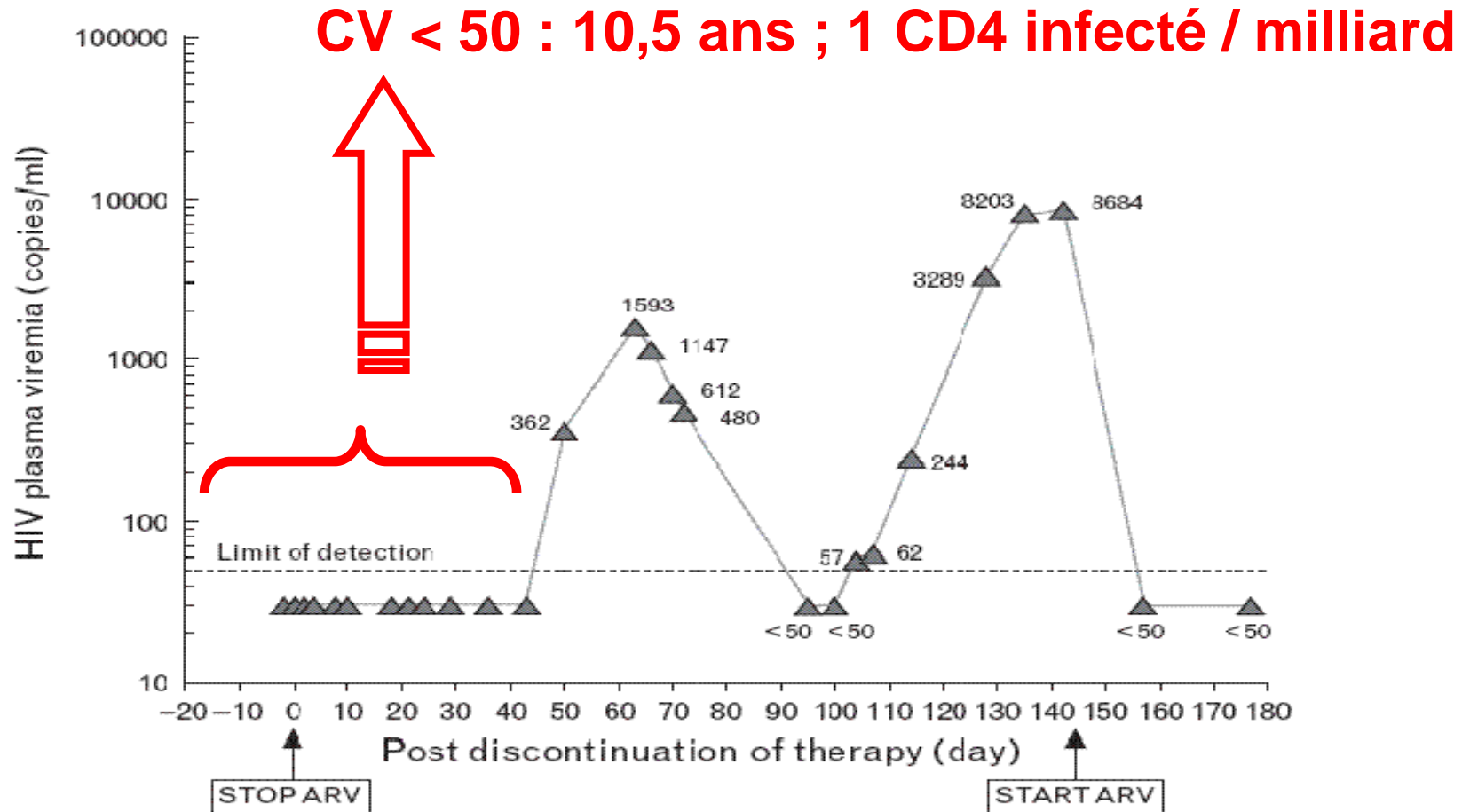


Latently infected resting memory
CD4⁺ T cells are the best-
characterized latent reservoir for HIV-1

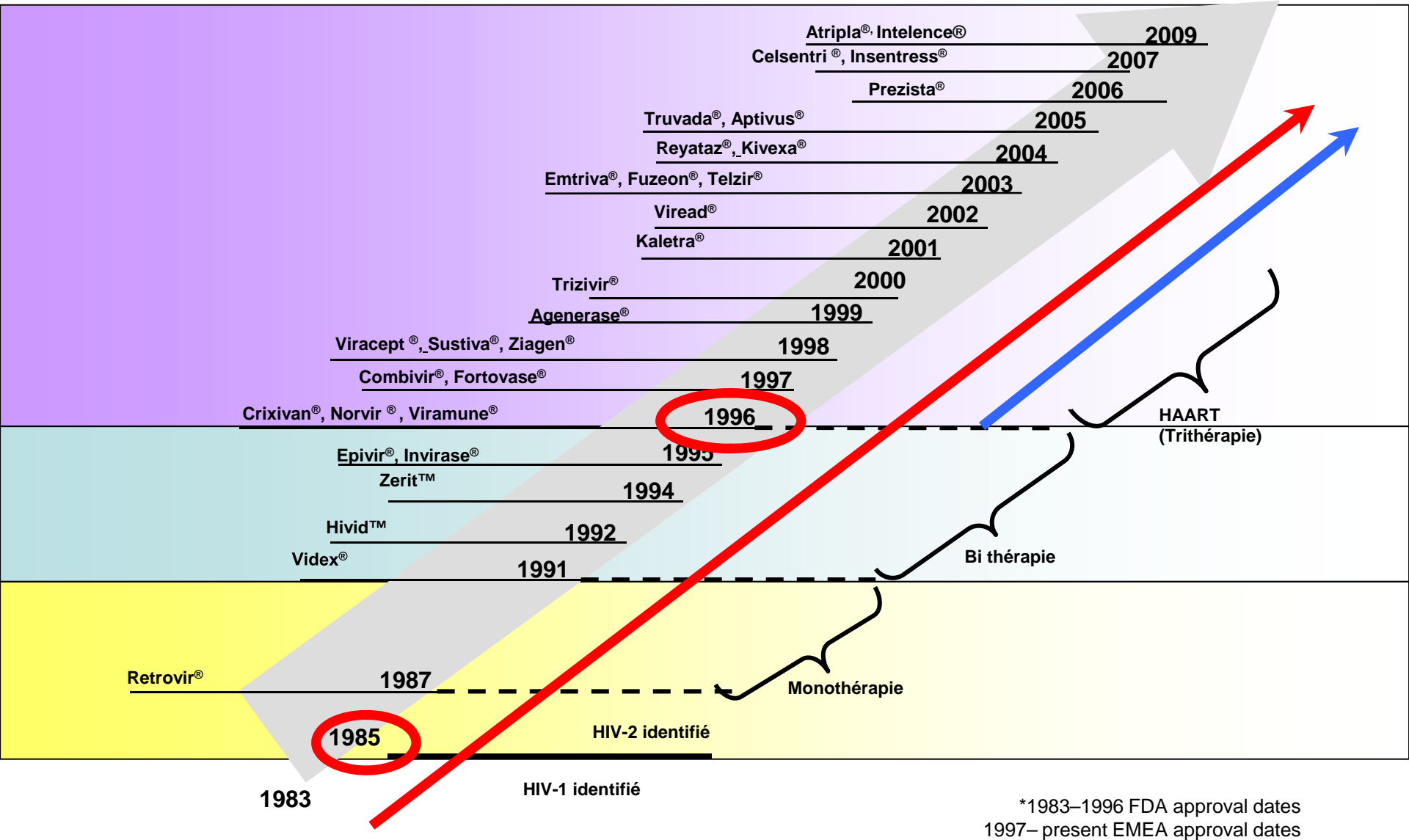


- ▶ « silent provirus : the **only known difference**
- ▶ **no markers** that can distinguish latently infected from uninfected cells »

Rebound of plasma viremia following cessation of antiretroviral therapy despite profoundly low levels of HIV reservoir: implications for eradication

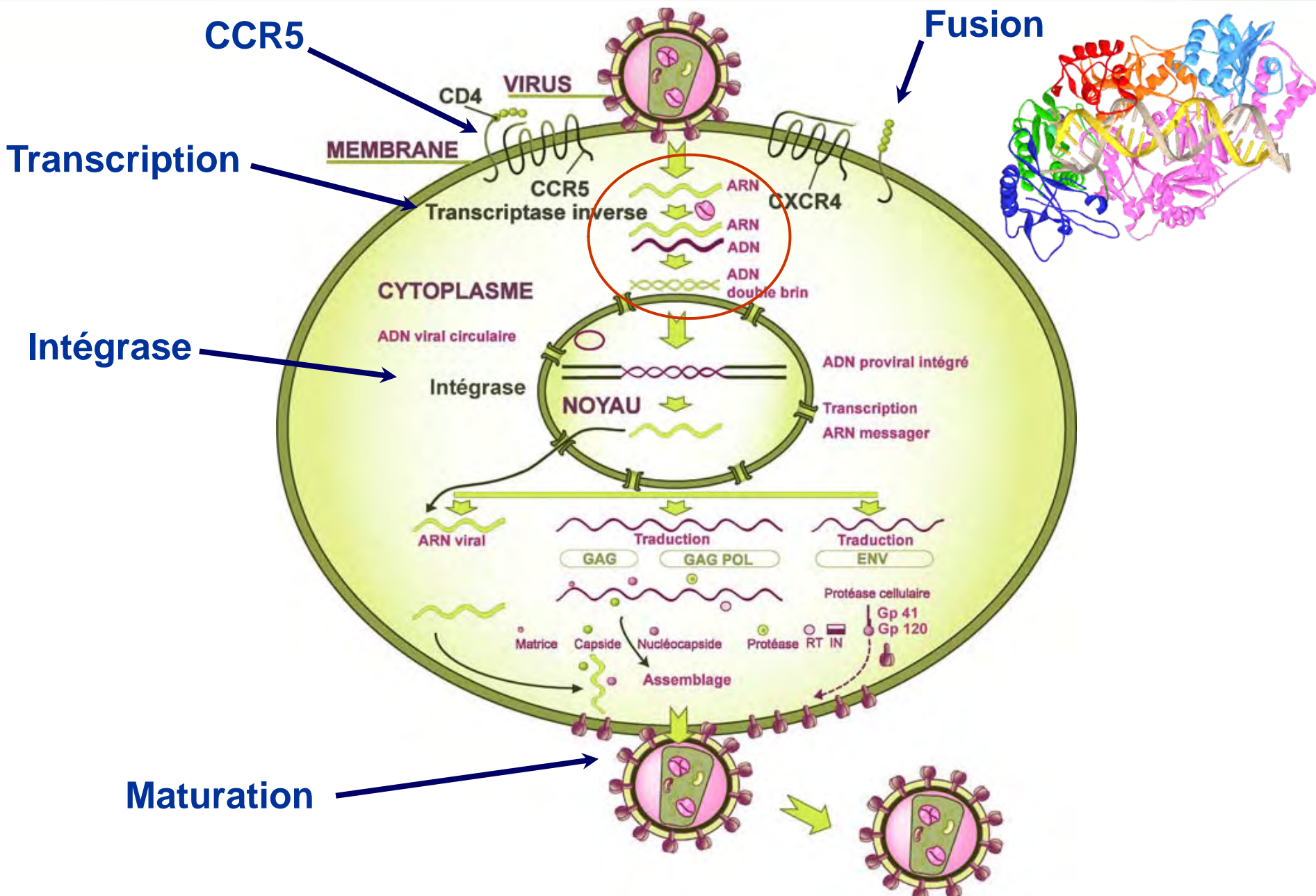
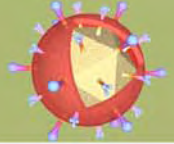


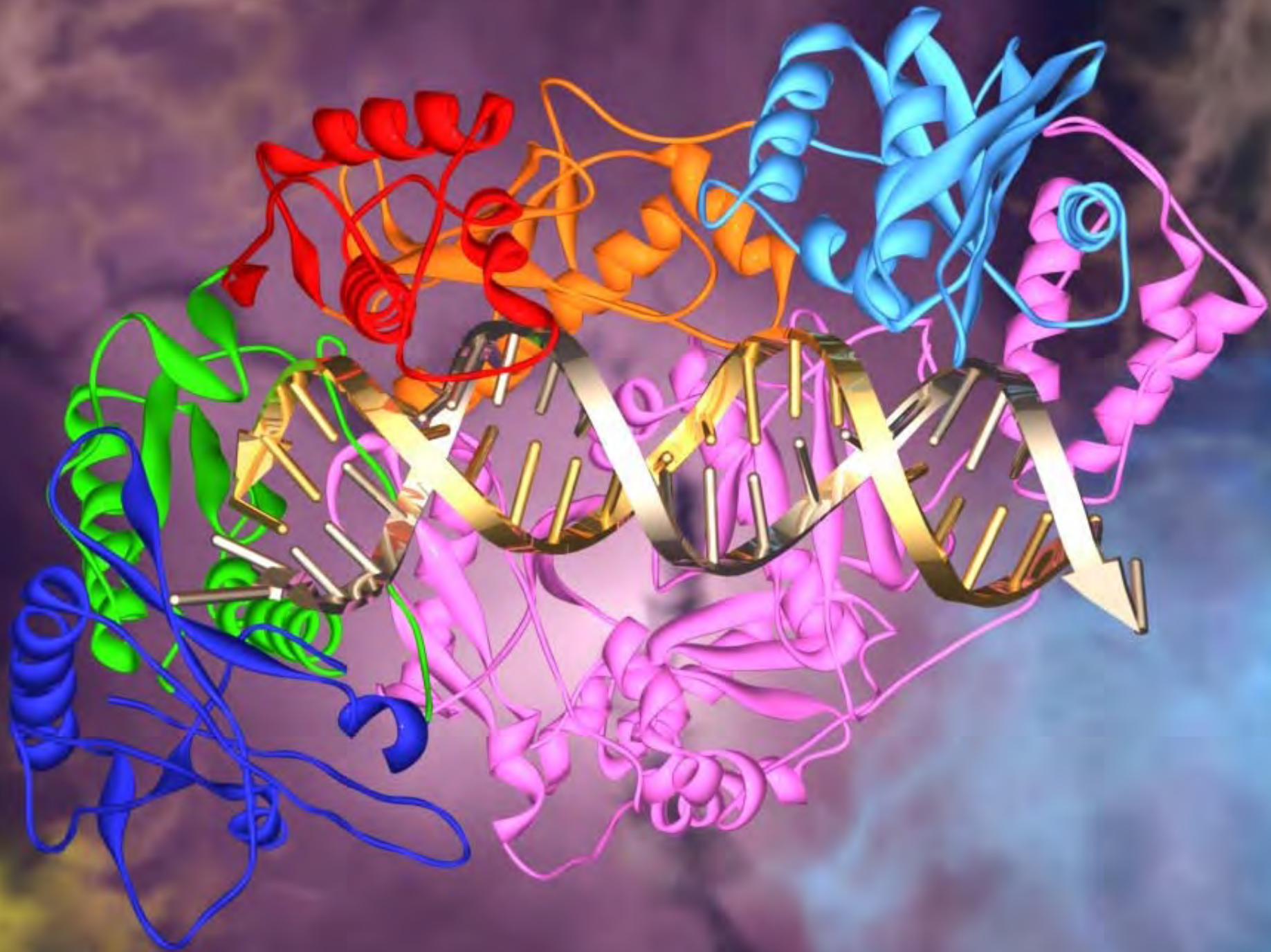
HISTORIQUE DES Antirétroviraux VIH



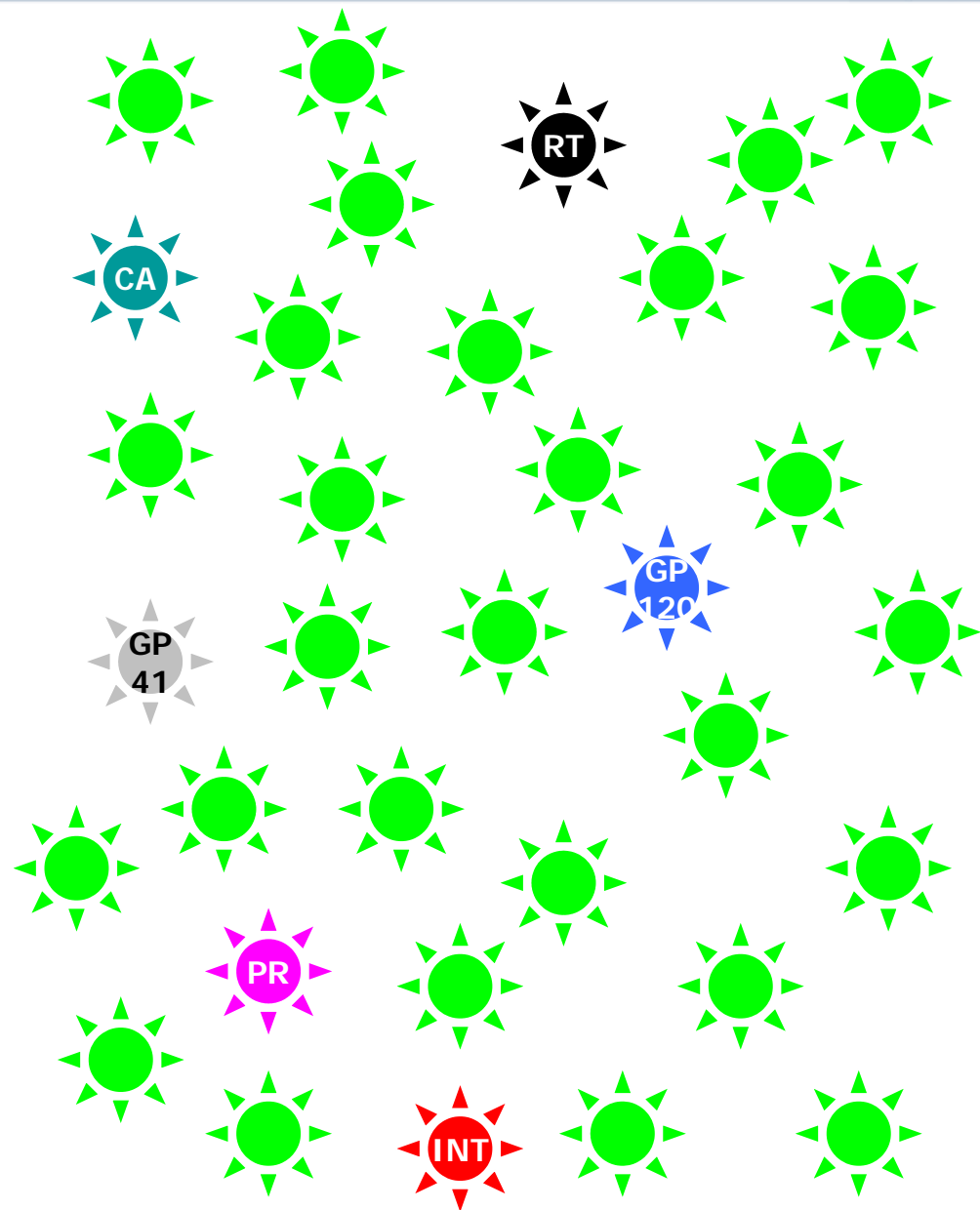
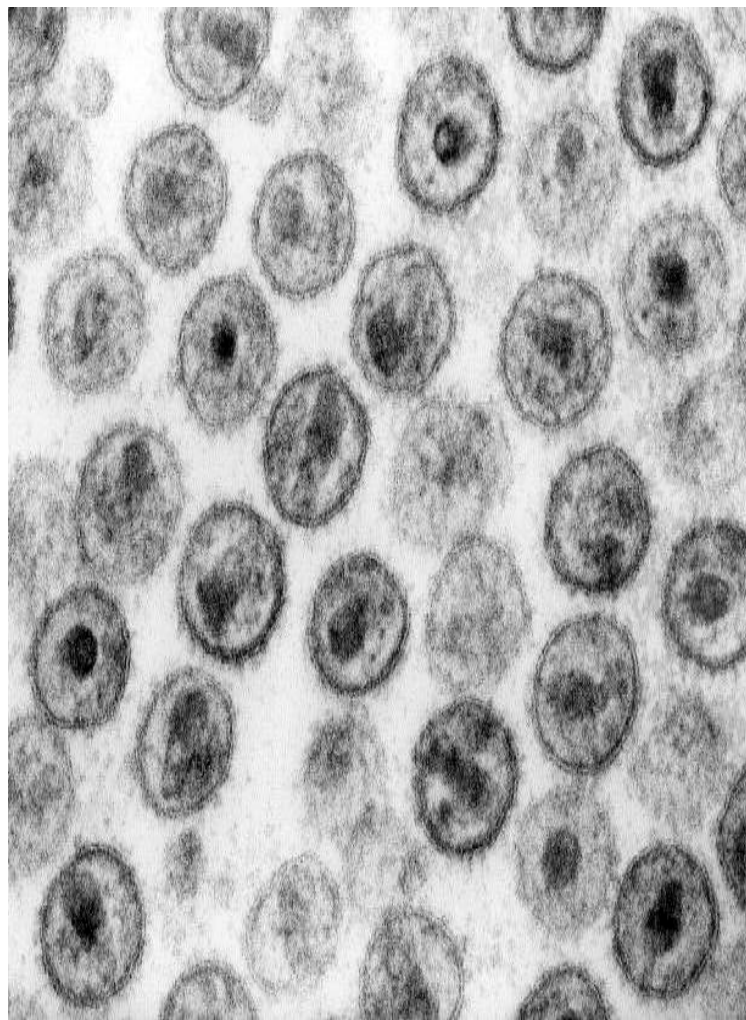
*1983–1996 FDA approval dates
1997– present EMEA approval dates

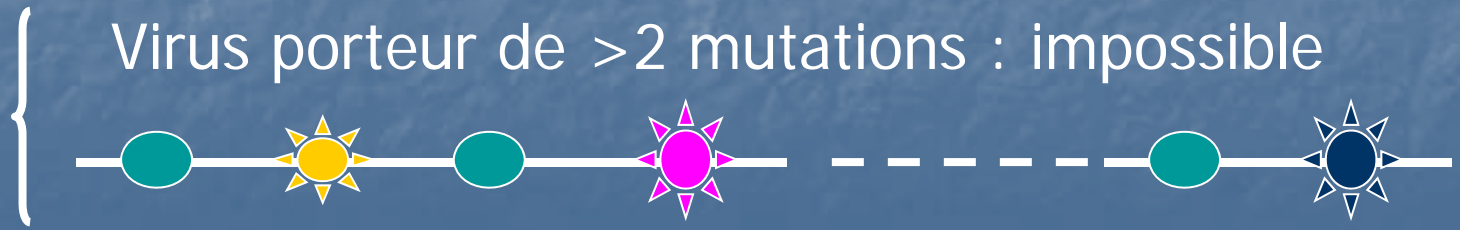
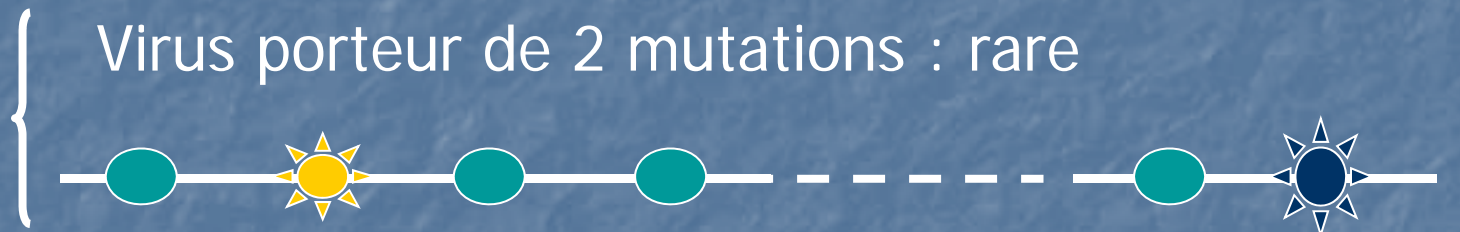
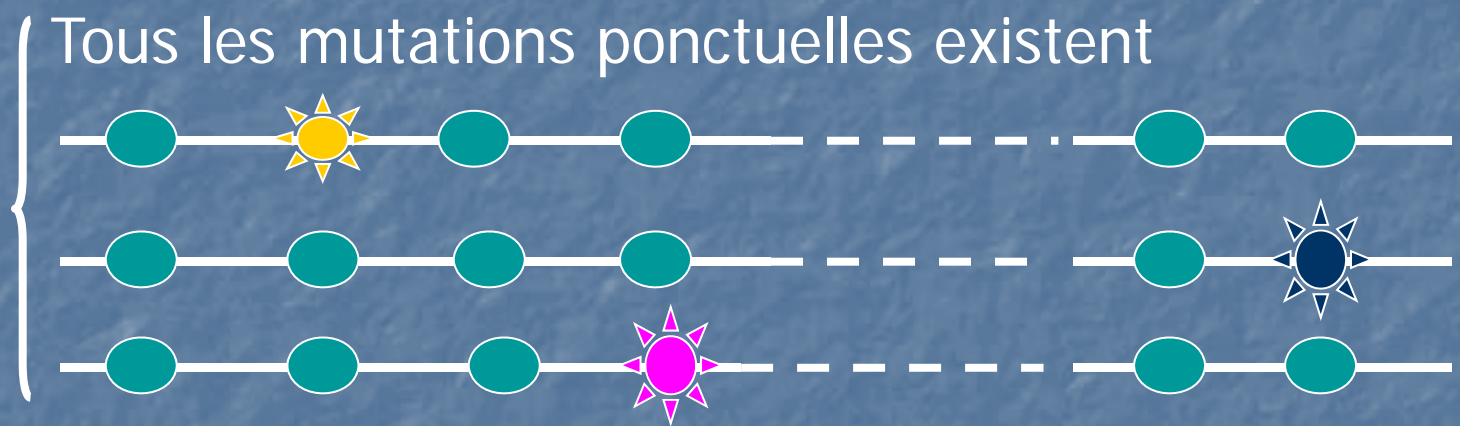
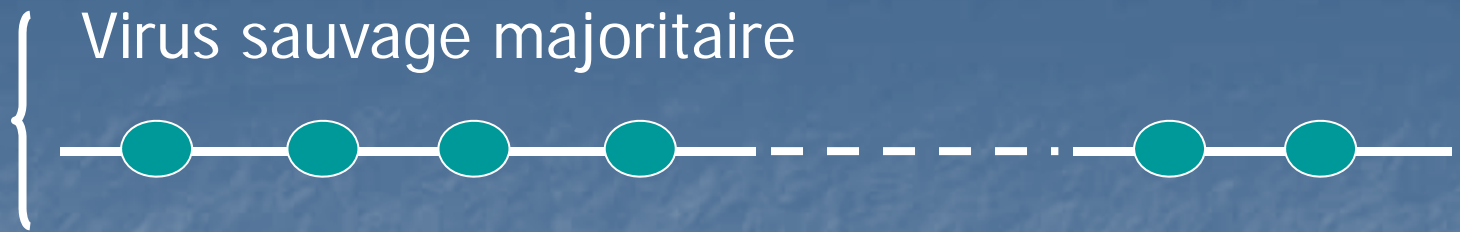
Cycle de réplication du VIH











Résistance virale



$$R = f (M \times E \times PS)$$

R : Résistance

M : Multiplication virale

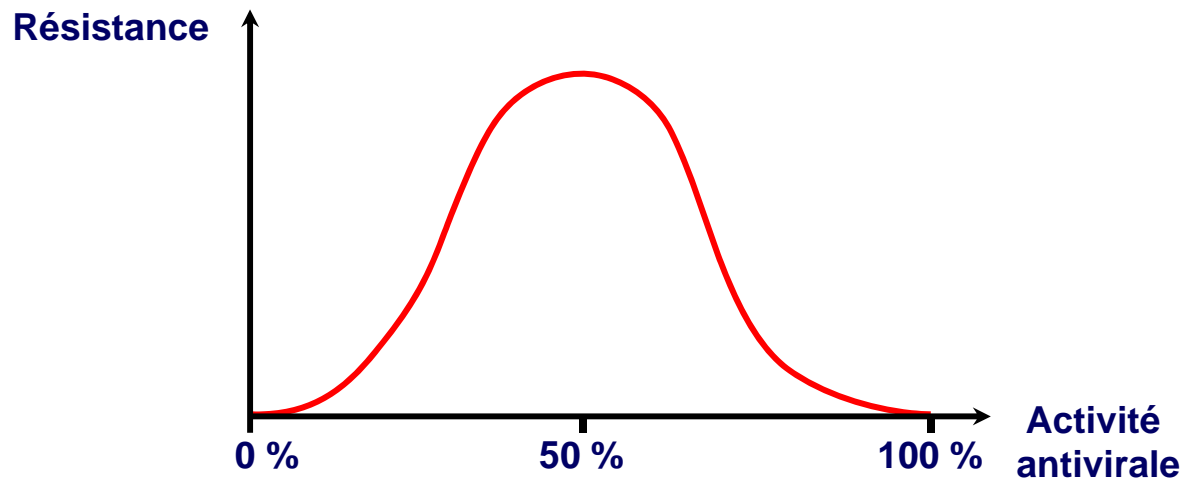
(≈ 10 milliards virus/jour ; « turn over rapide »)

E : Erreurs de la RT

(≈ 1 erreur / 10.000 paires de base)

PS : Pression de sélection

(ex : traitement)



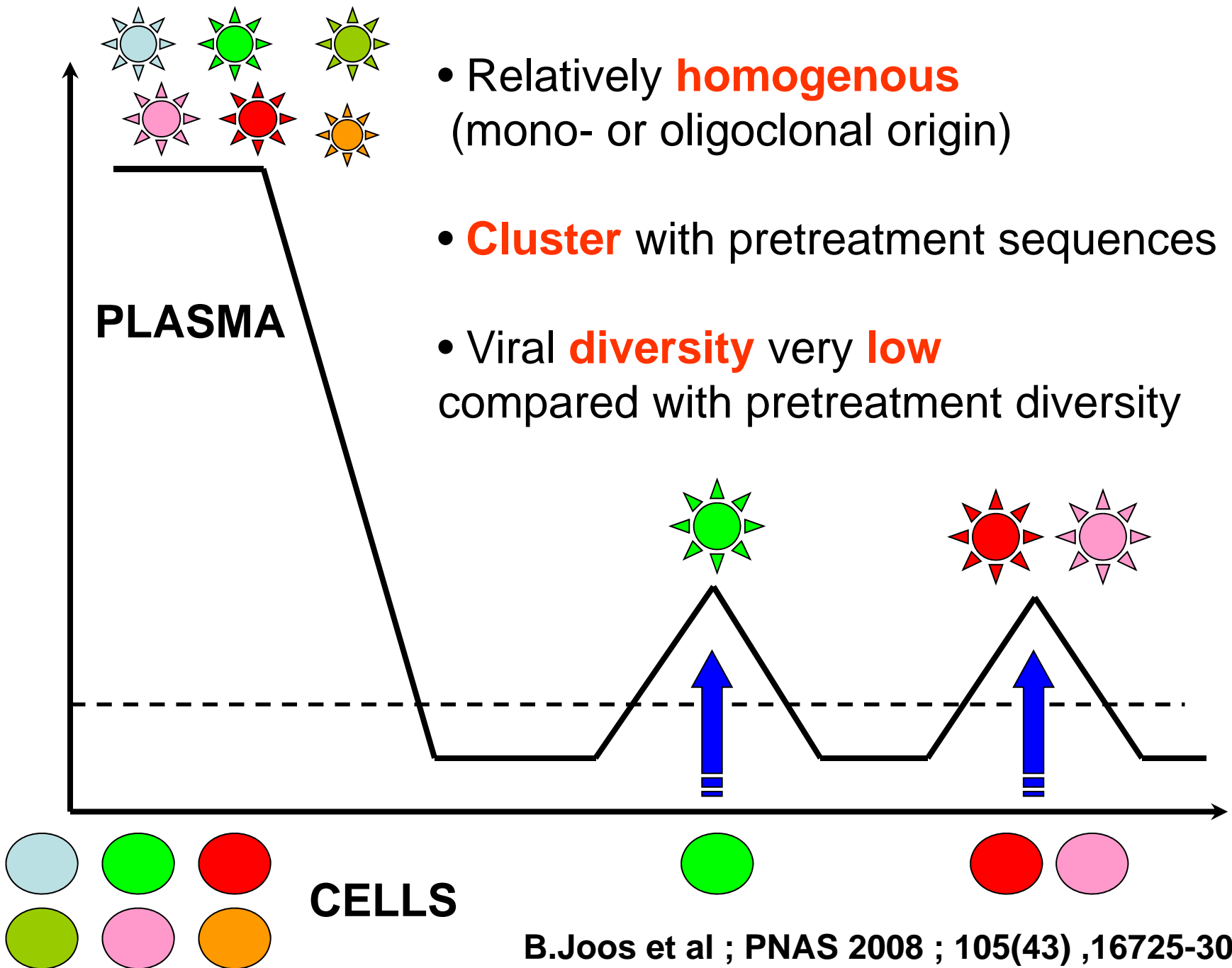
Réplication résiduelle sous traitement

HIV rebounds from latently infected cells, rather than from continuing low-level replication

20 patients (VL<50) ; multiple 2-week STI's

Clonal evolutionary studies

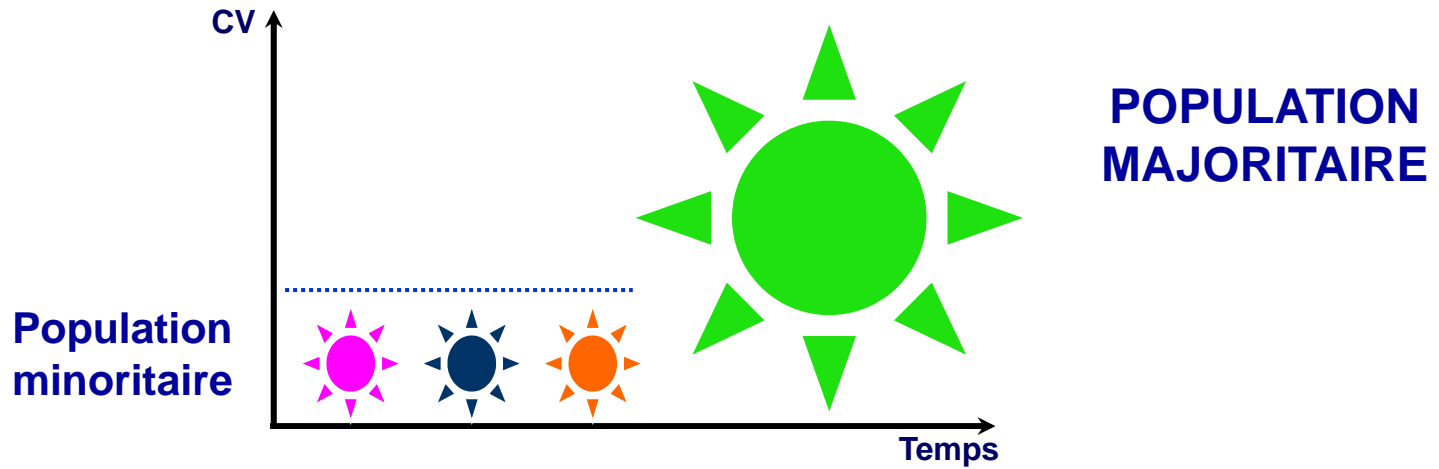
of « rebounding plasma virus » (C2-V3-C3)



Résistance virale

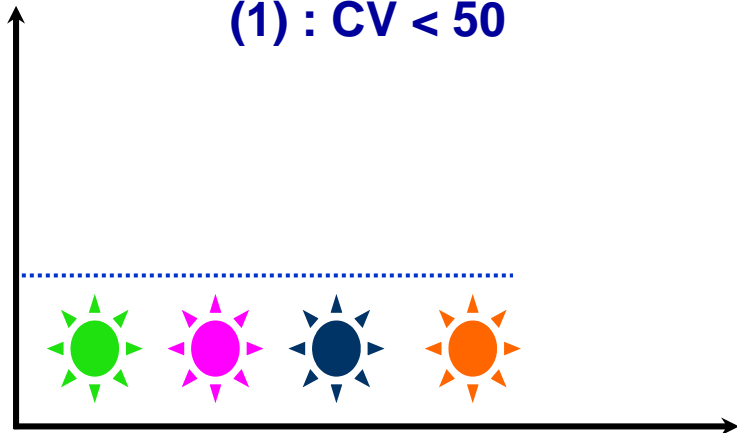


PATIENT NON TRAITE

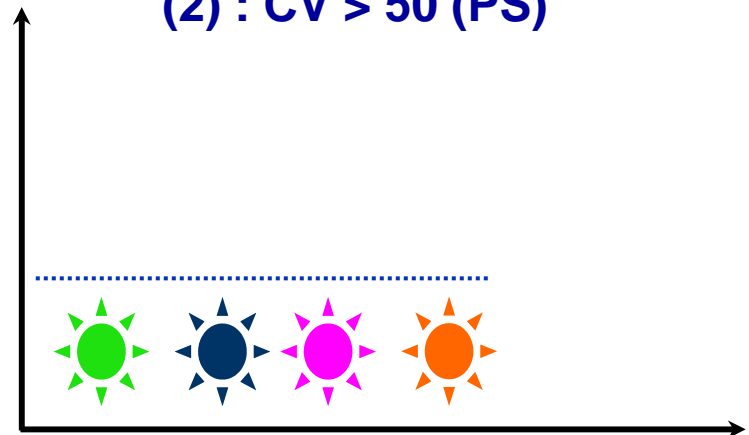


PATIENT TRAITE

(1) : $CV < 50$



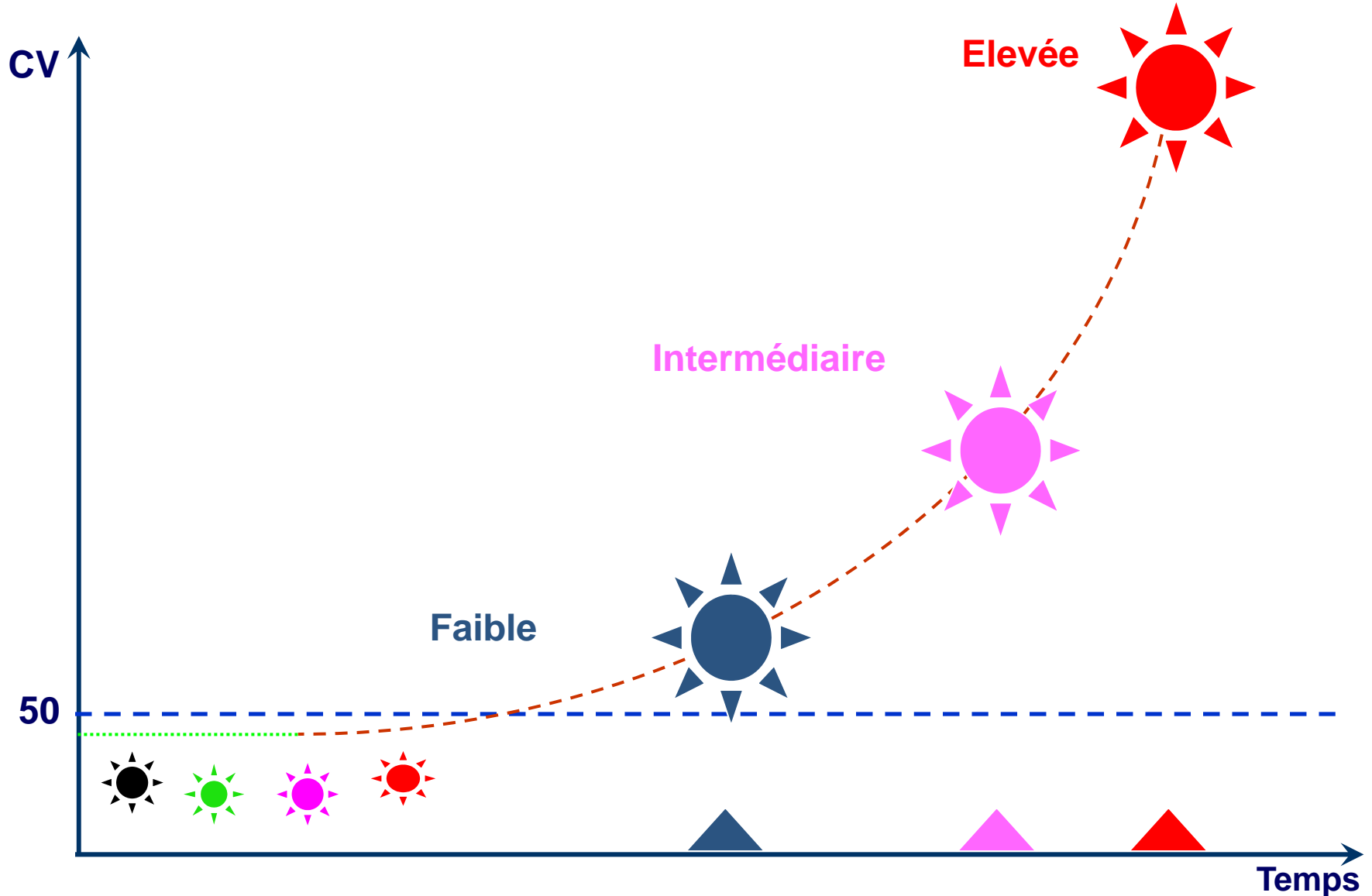
(2) : $CV > 50$ (PS)



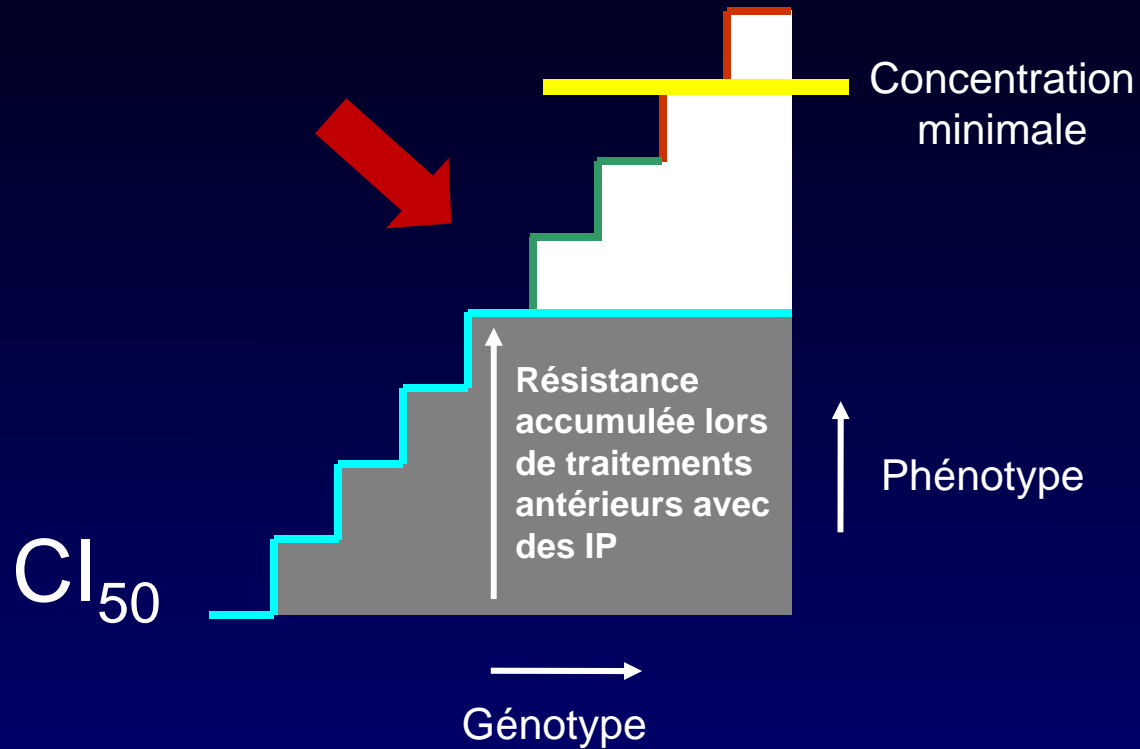
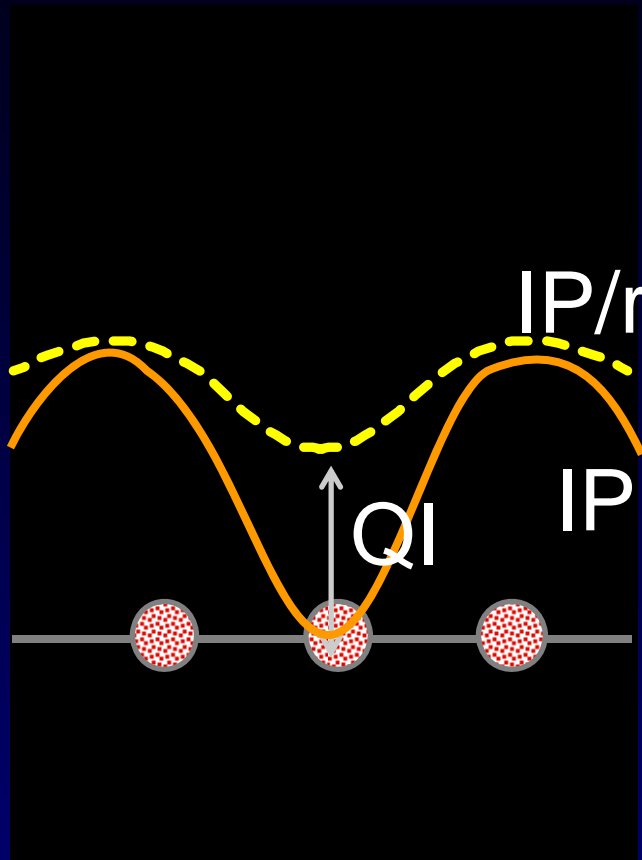
Résistance virale



✓ Echec virologique et barrière génétique



Quotient inhibiteur (QI) et barrière génétique



$$QI = C_{\min} : CI_{50}$$

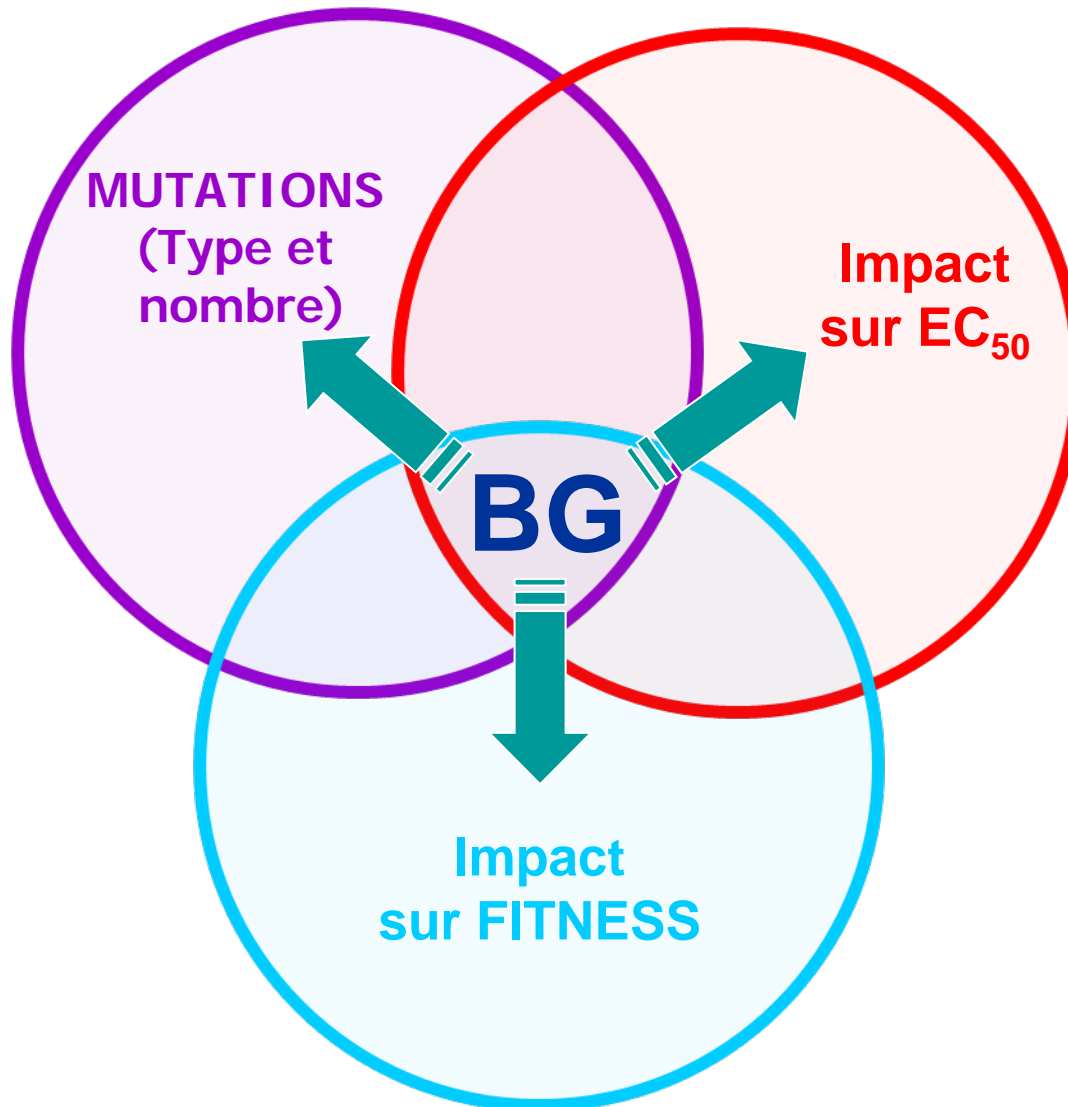
Mesure pharmacocinétique de l'inhibition virale

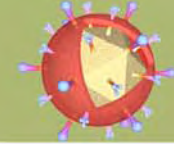
La résistance aux IP est un processus progressif

Résistance virale



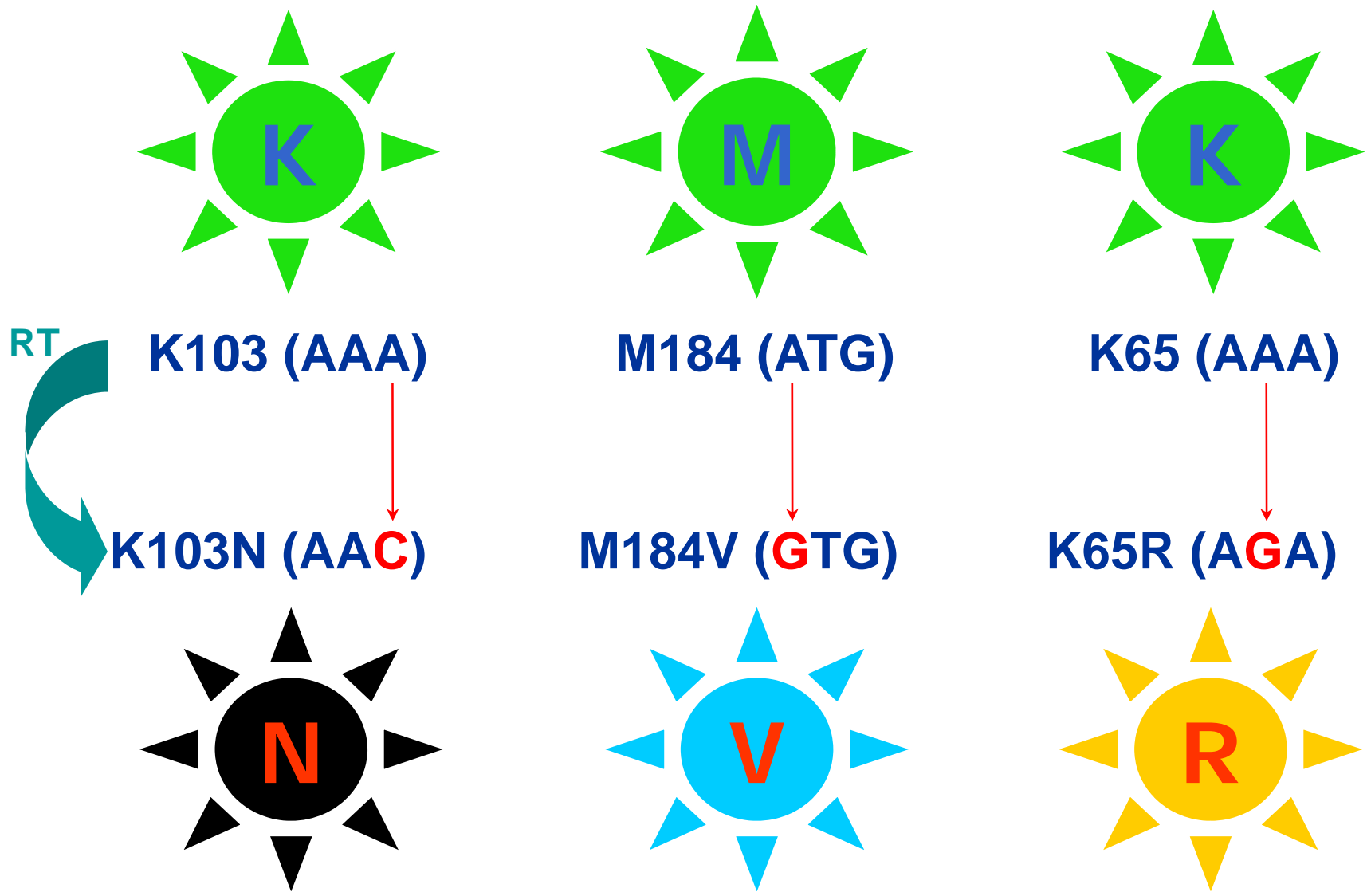
✓ Echec virologique et barrière génétique

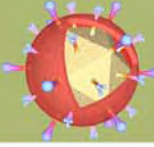




Résistance virale

✓ Echec virologique et barrière génétique





Résistance virale

✓ Echec virologique et barrière génétique

⌘ Une seule mutation pour obtenir :

K103N



EFV

M184V



3TC/FTC

K65R



TDF



**Barrières
génétiques
identiques???**



Résistance virale

✓ Echec virologique et barrière génétique

⌘ Etude GS-01-934 : Patients en échecs

TDF+FTC+EFV

19/244 (7,8%)

K103N

42,1%



Résistance virale

✓ Echec virologique et barrière génétique

⌘ Etude GS-01-934 : Patients en échecs

TDF+FTC+EFV

19/244 (7,8%)

K103N

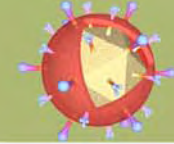
42,1%

M184V/I

10,5%

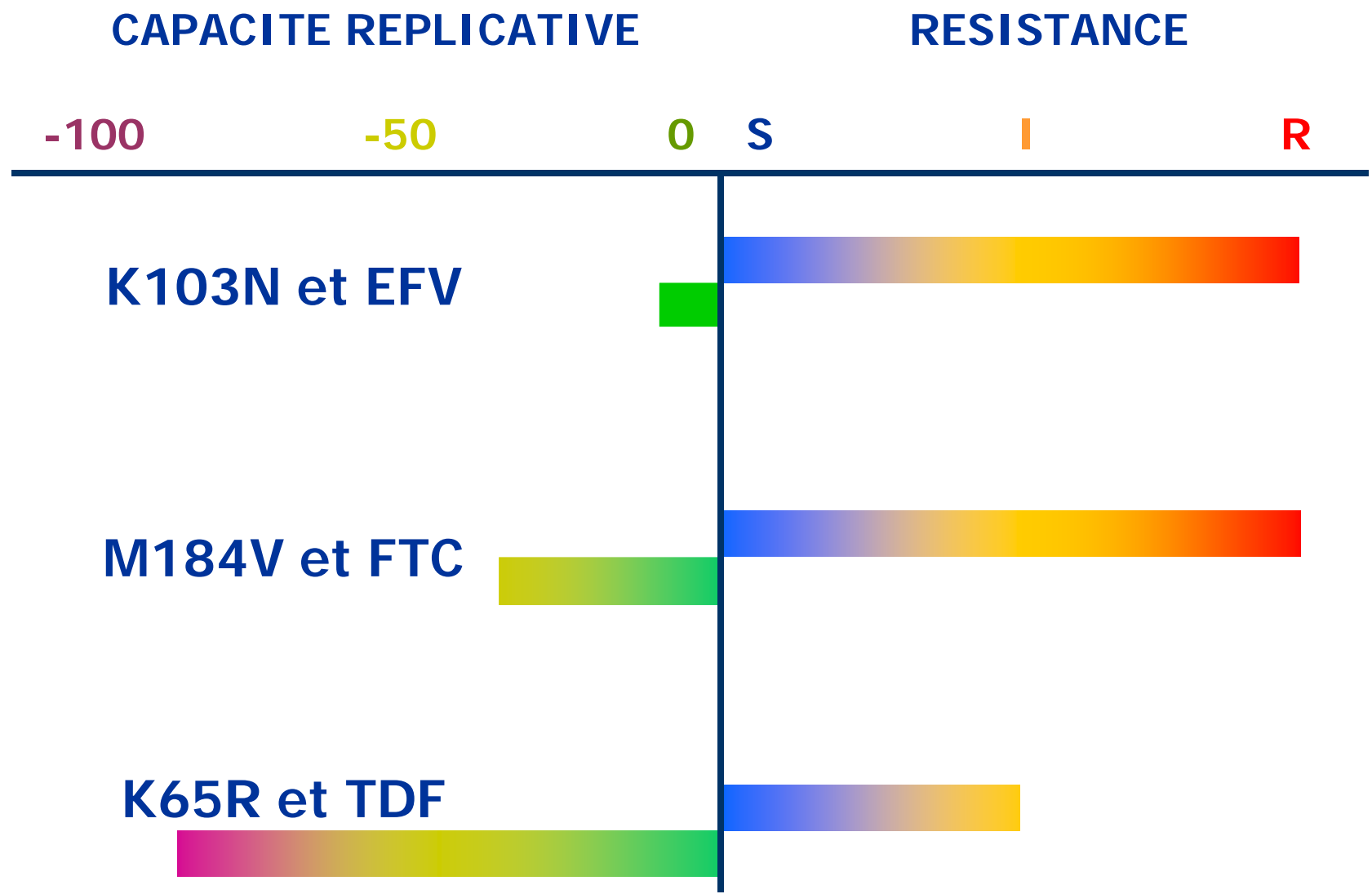
K65R

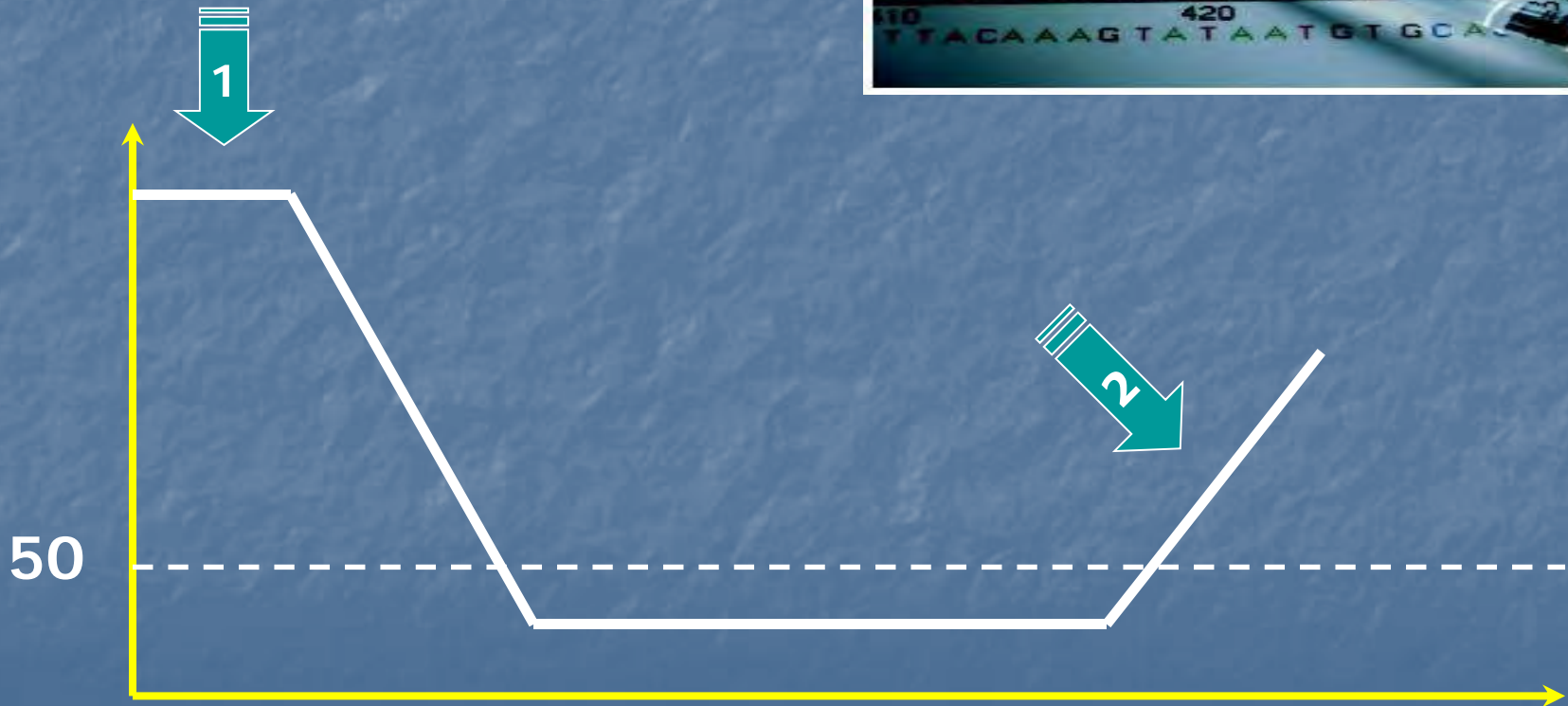
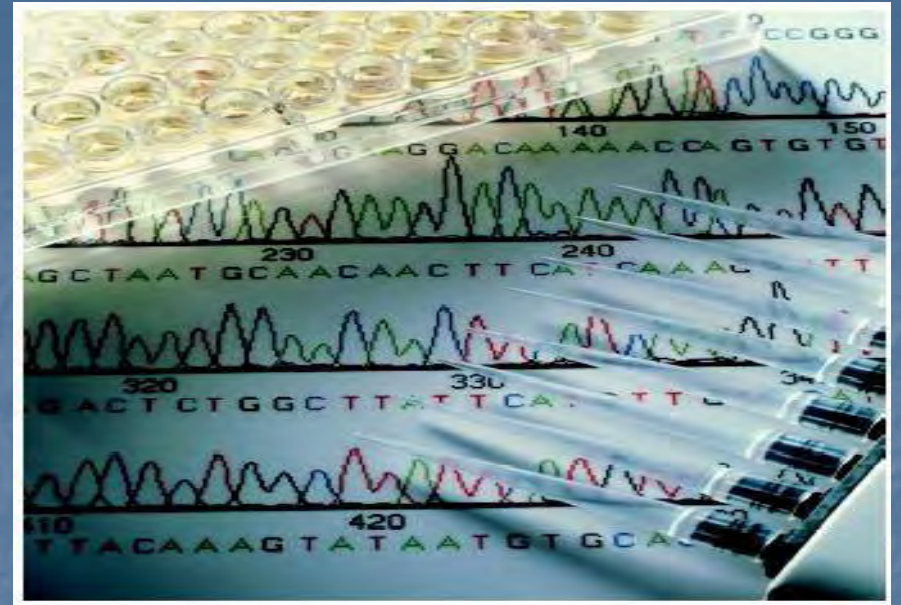
0%



Résistance virale

✓ Echec virologique et barrière génétique

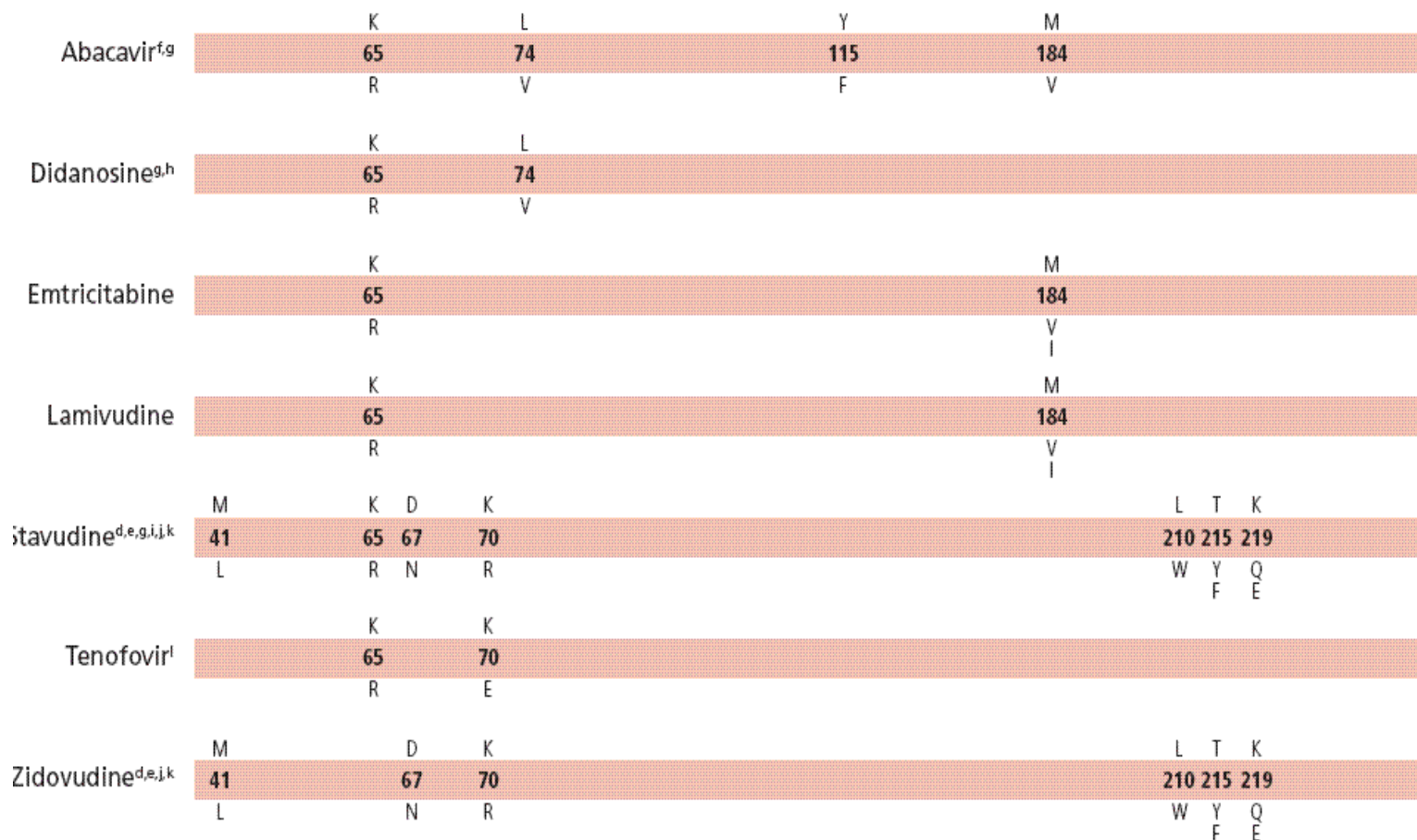






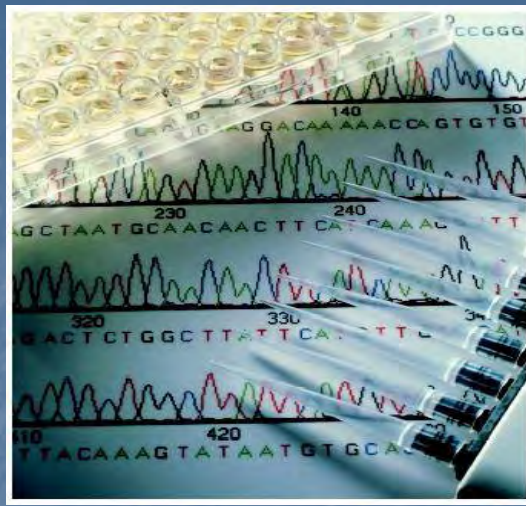
Update of the Drug Resistance Mutations in HIV-1: December 2010

V.A Johnson et al ; Topics in HIV Medicine 2010



Indications des tests génotypiques de résistance

Situation Clinique	Recommandation (Niveau de preuve)
Primo-infection et infection récente (< 6 mois)	Recommandé (AII)
Avant l'initiation du traitement : – à la découverte de la séropositivité – sinon sur le prélèvement disponible le plus ancien – ou avant de débiter le traitement	Recommandé (AII)
Échecs thérapeutiques	Recommandé (AI)
Prophylaxie post-exposition	A réaliser au cas par cas
Enfants	Mêmes indications que chez l'adulte (AII)
Grossesse	Recommandé (AII)

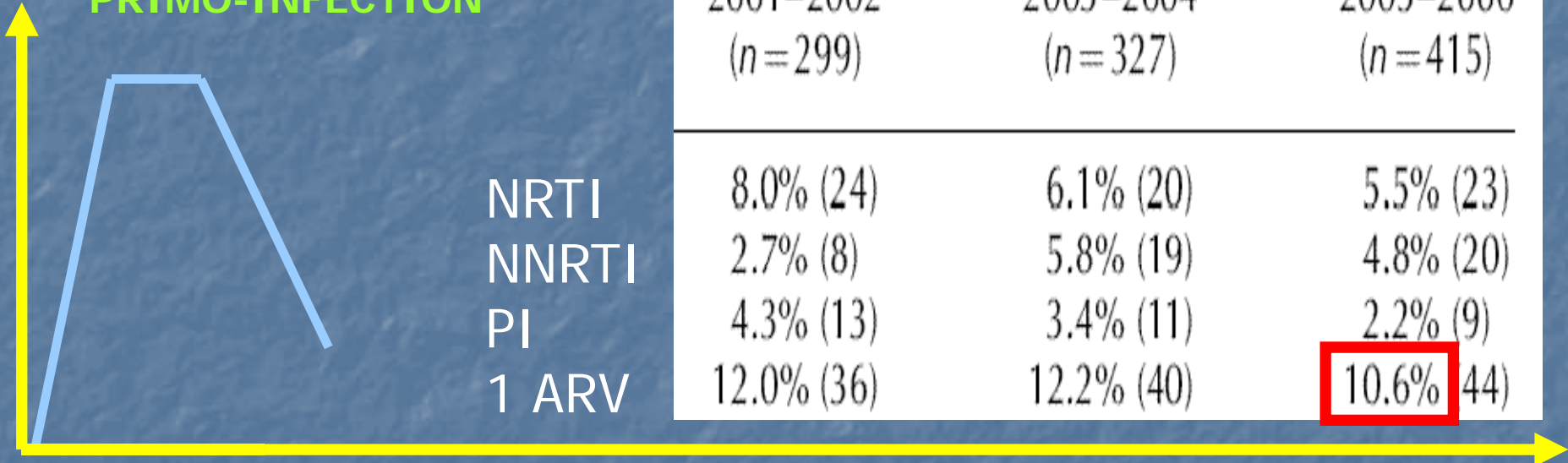


GENOTYPE CHEZ LE PATIENT NAIF

Stable frequency of HIV-1 transmitted drug resistance in patients at the time of primary infection over 1996–2006 in France

M.L Chaix et al ; AIDS 2009

PRIMO-INFECTION

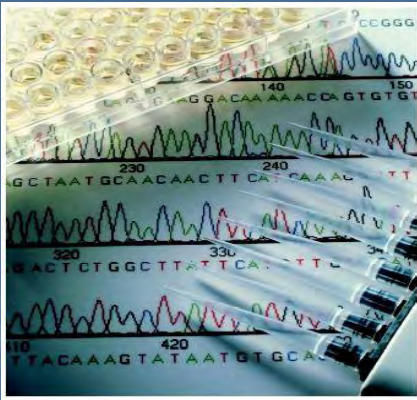


NRTI
NNRTI
PI
1 ARV

	2001–2002 (n=299)	2003–2004 (n=327)	2005–2006 (n=415)
NRTI	8.0% (24)	6.1% (20)	5.5% (23)
NNRTI	2.7% (8)	5.8% (19)	4.8% (20)
PI	4.3% (13)	3.4% (11)	2.2% (9)
1 ARV	12.0% (36)	12.2% (40)	10.6% (44)

Transmission of Drug-Resistant HIV-1 Is Stabilizing in Europe

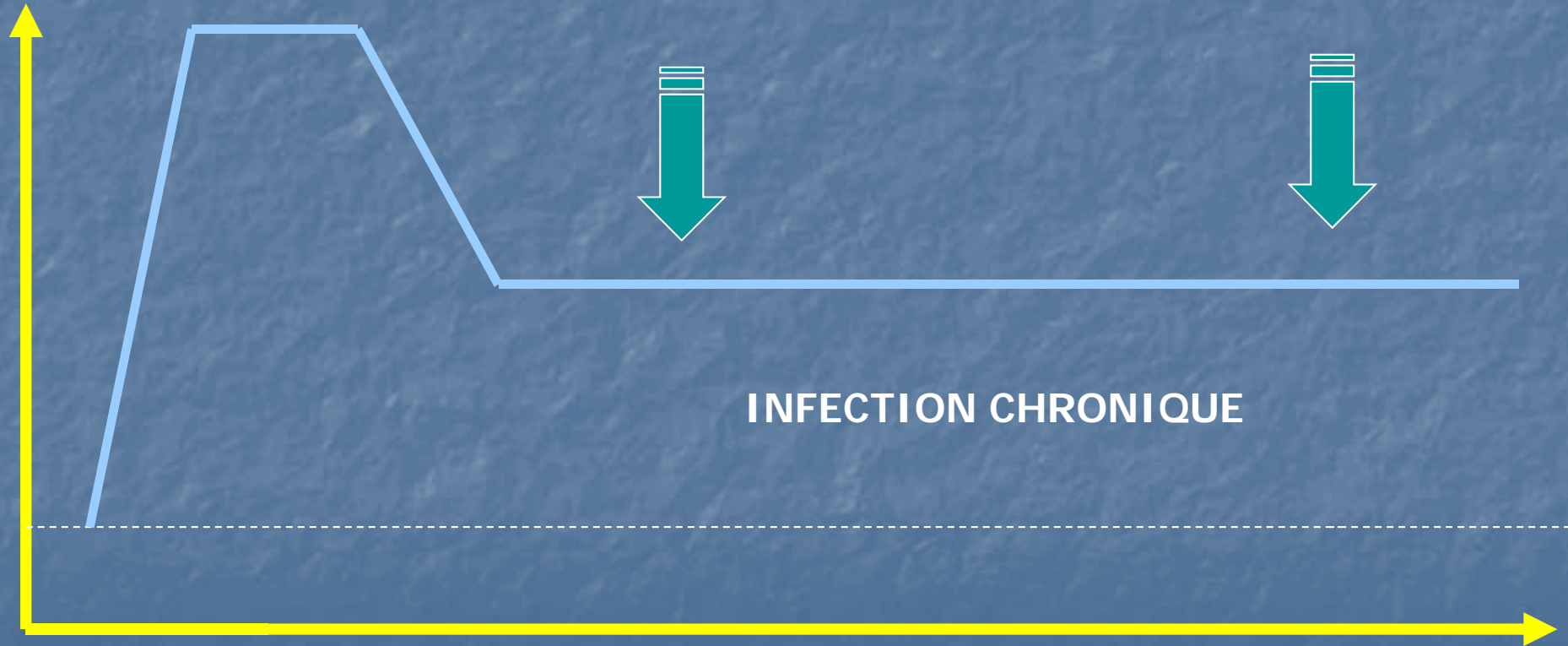
J.Vercauteren et al ;
JID 2009

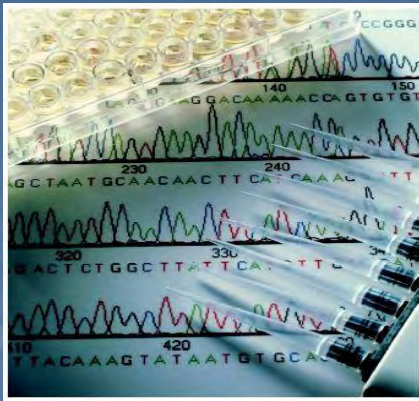


GENOTYPE CHEZ LE PATIENT NAIF

**DECOUVERTE DE
LA SEROPOSITIVITE**

**INITIATION
DU TRAITEMENT**



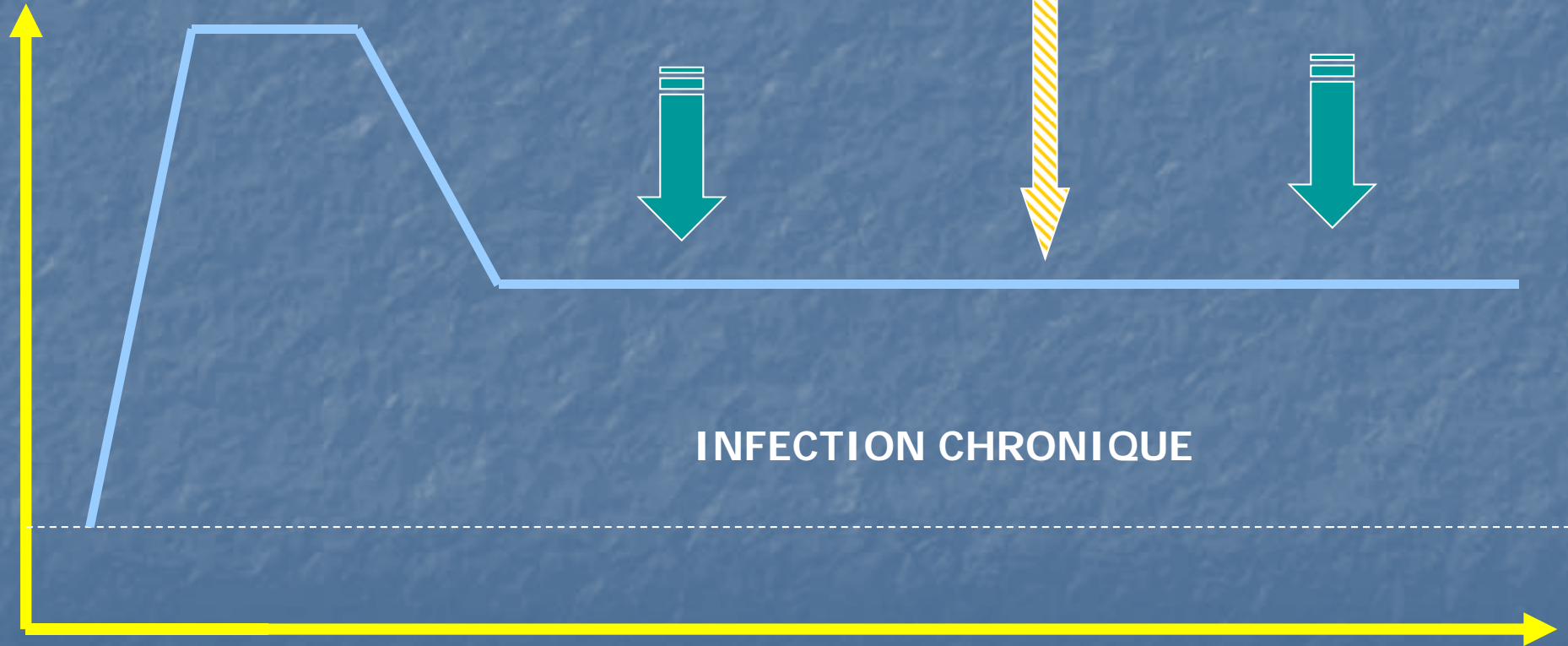


GENOTYPE CHEZ LE PATIENT NAIF

RISQUE DE SURINFECTION

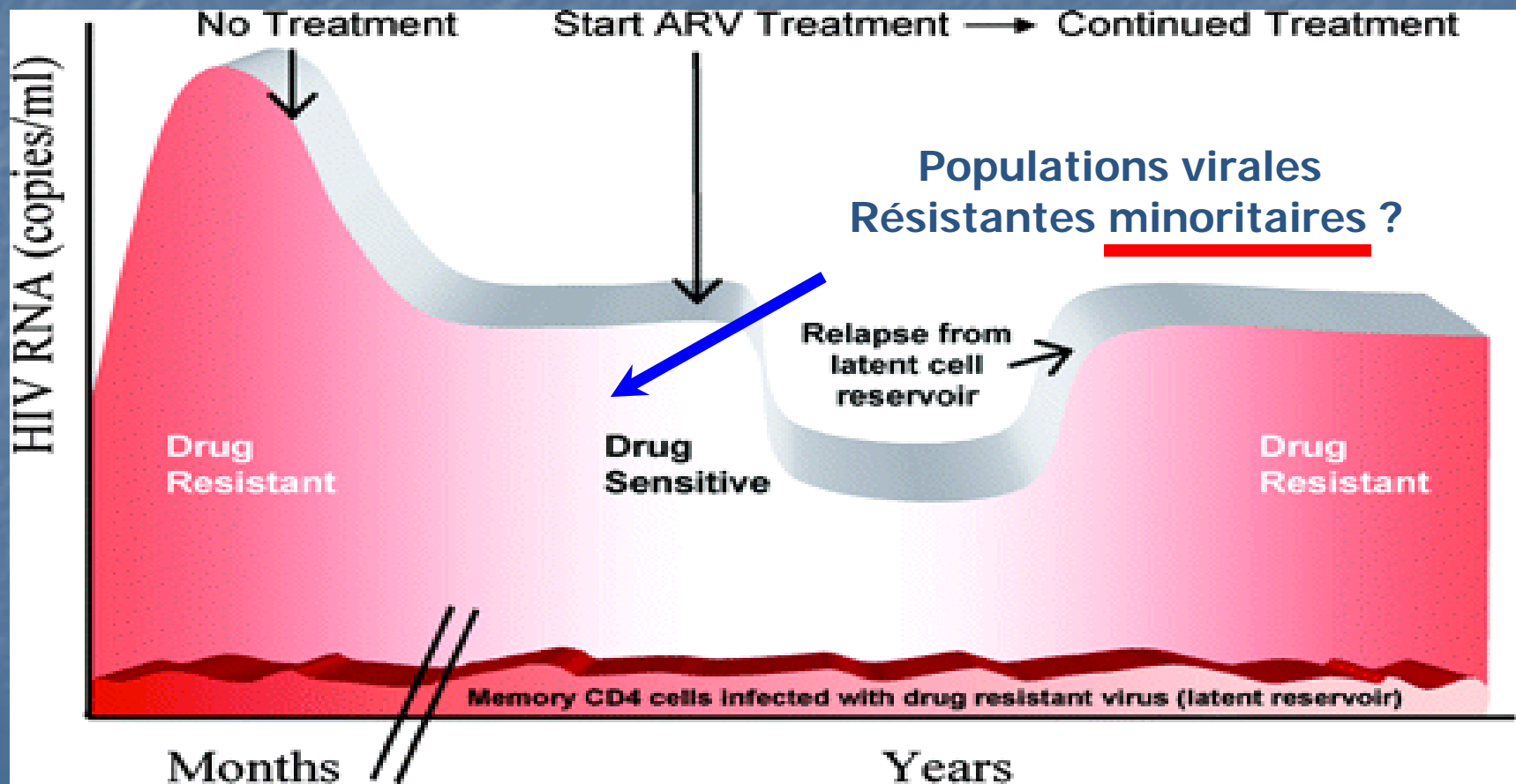
DECOUVERTE DE LA SEROPOSITIVITE

INITIATION DU TRAITEMENT

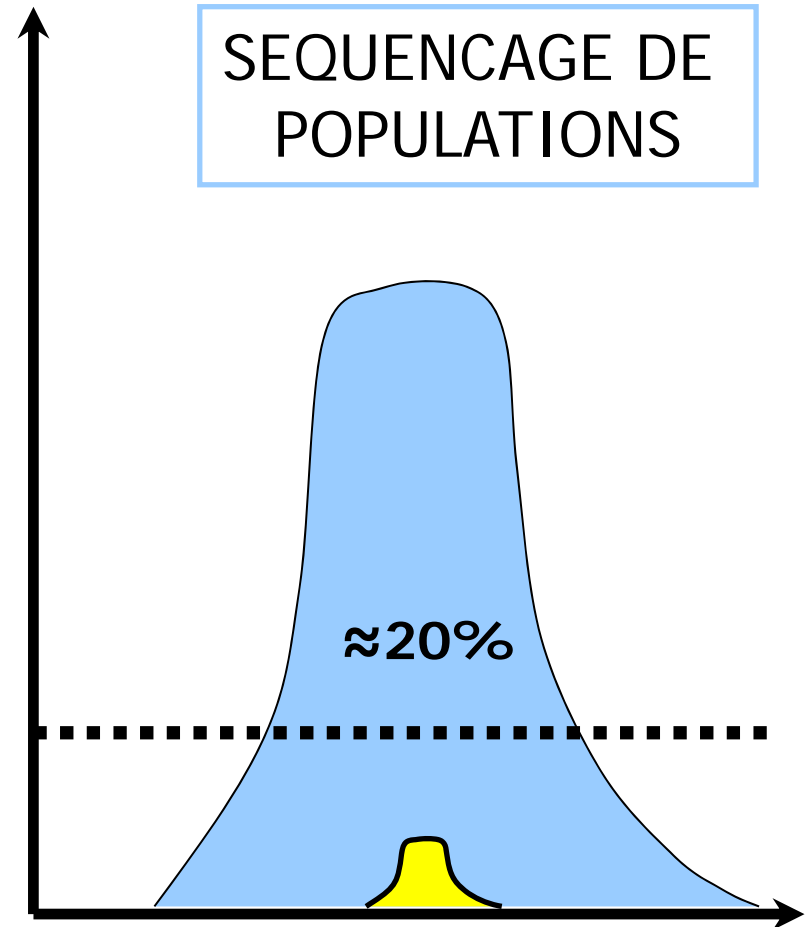


Persistence of Transmitted Drug Resistance among Subjects with Primary Human Immunodeficiency Virus Infection[▽]

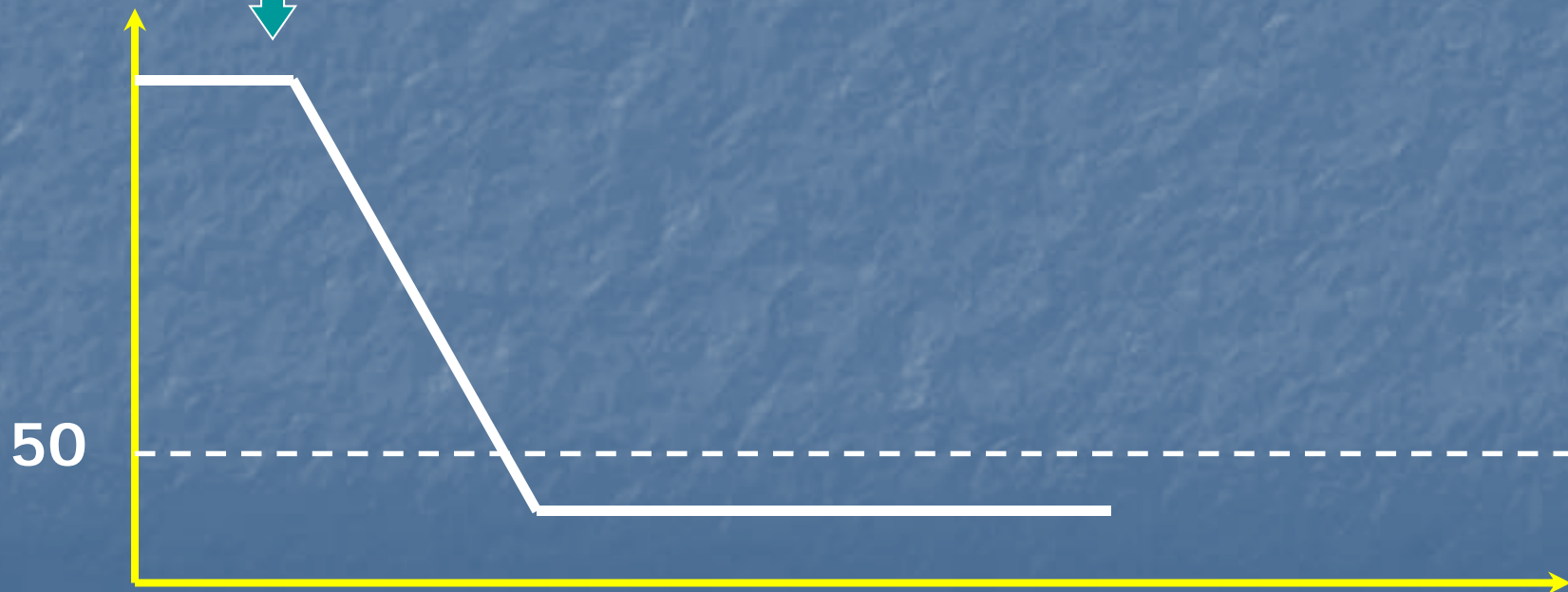
S.J Little et al ; J.Virol 2008



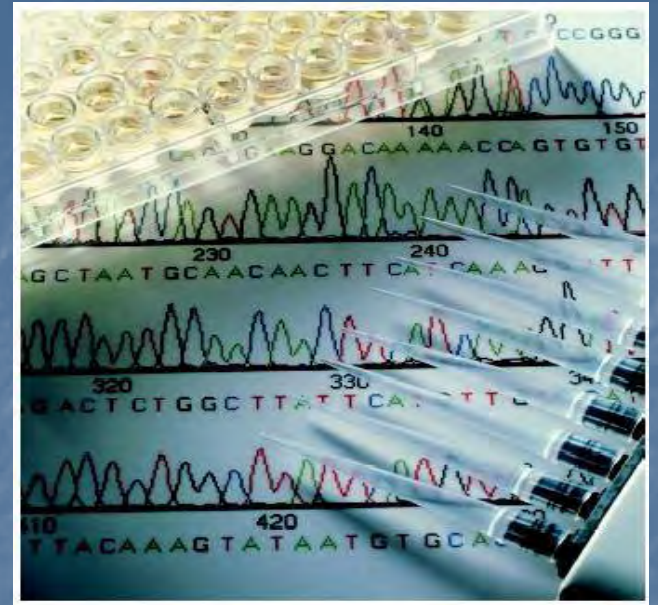
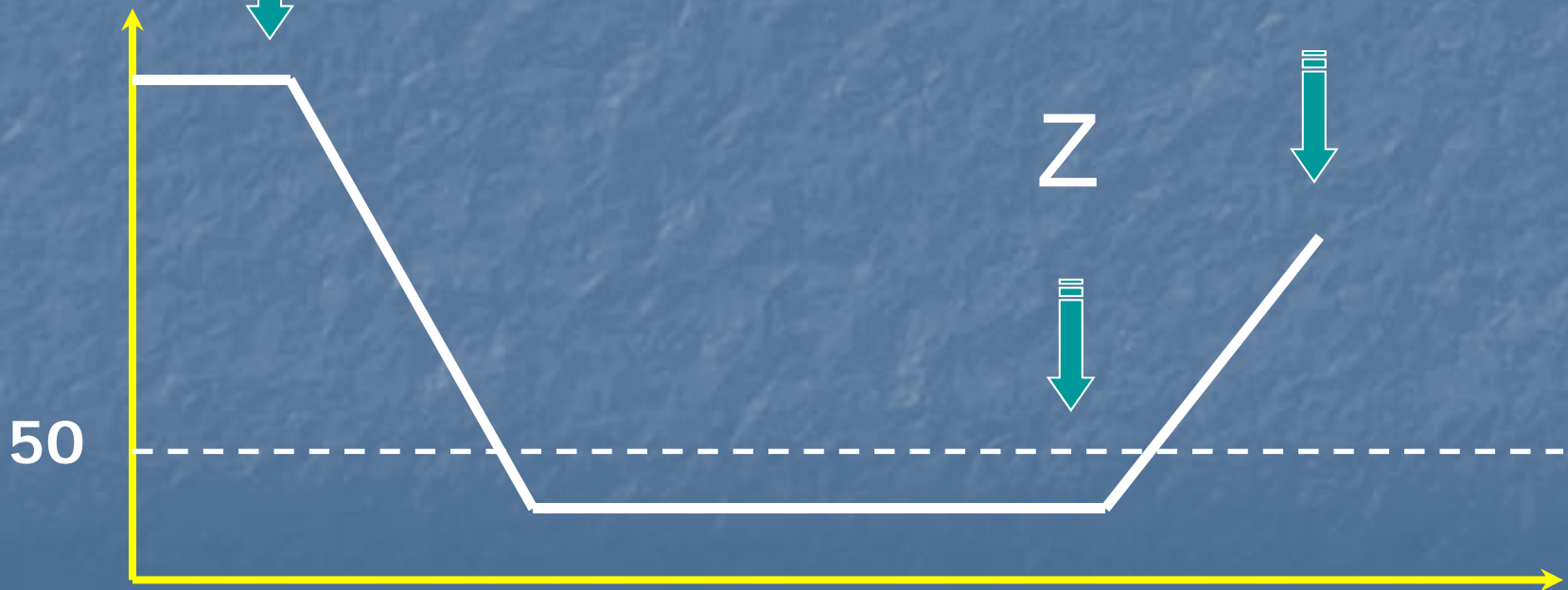
Populations virales minoritaires



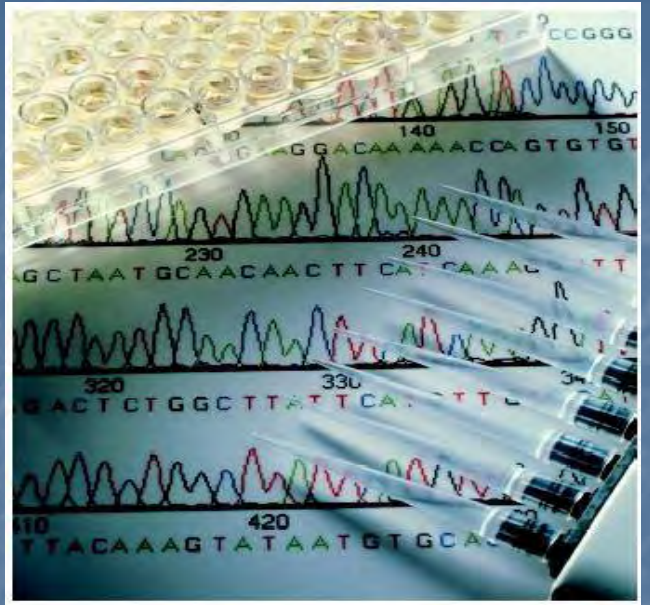
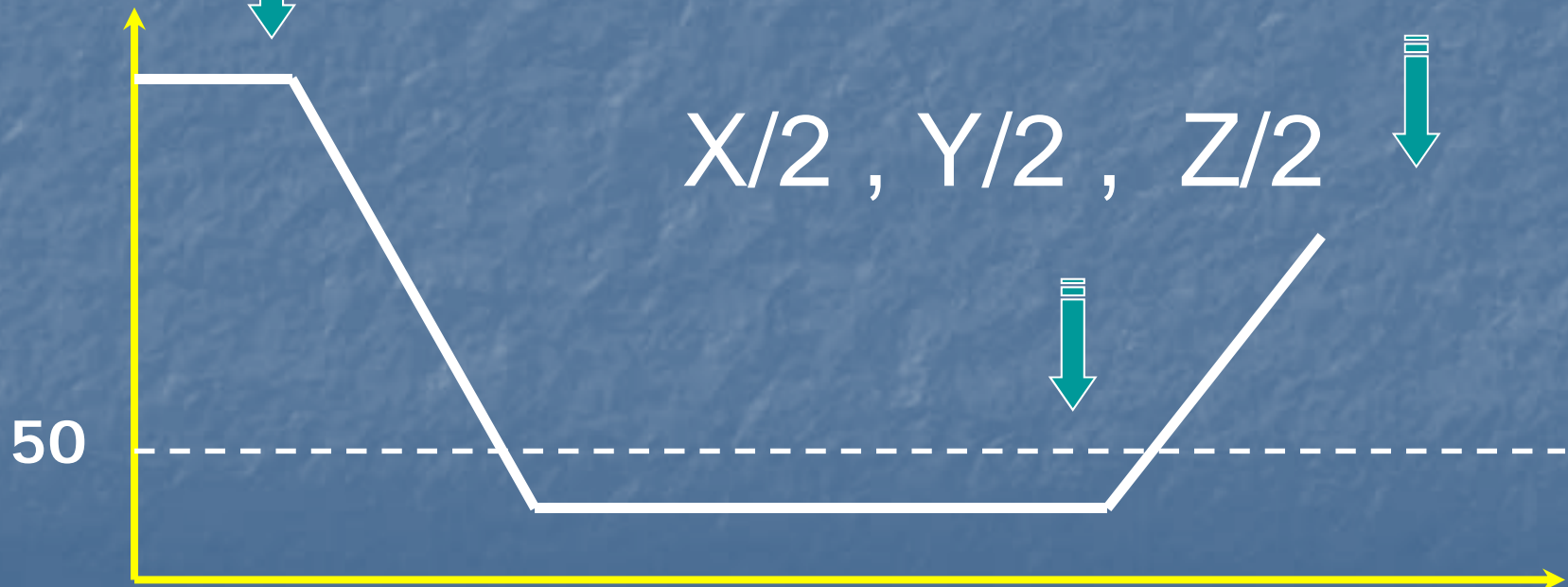
X, Y, Z



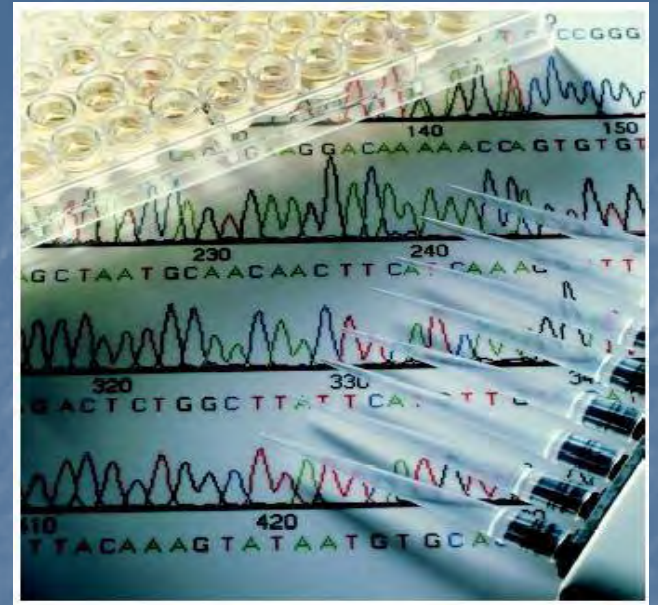
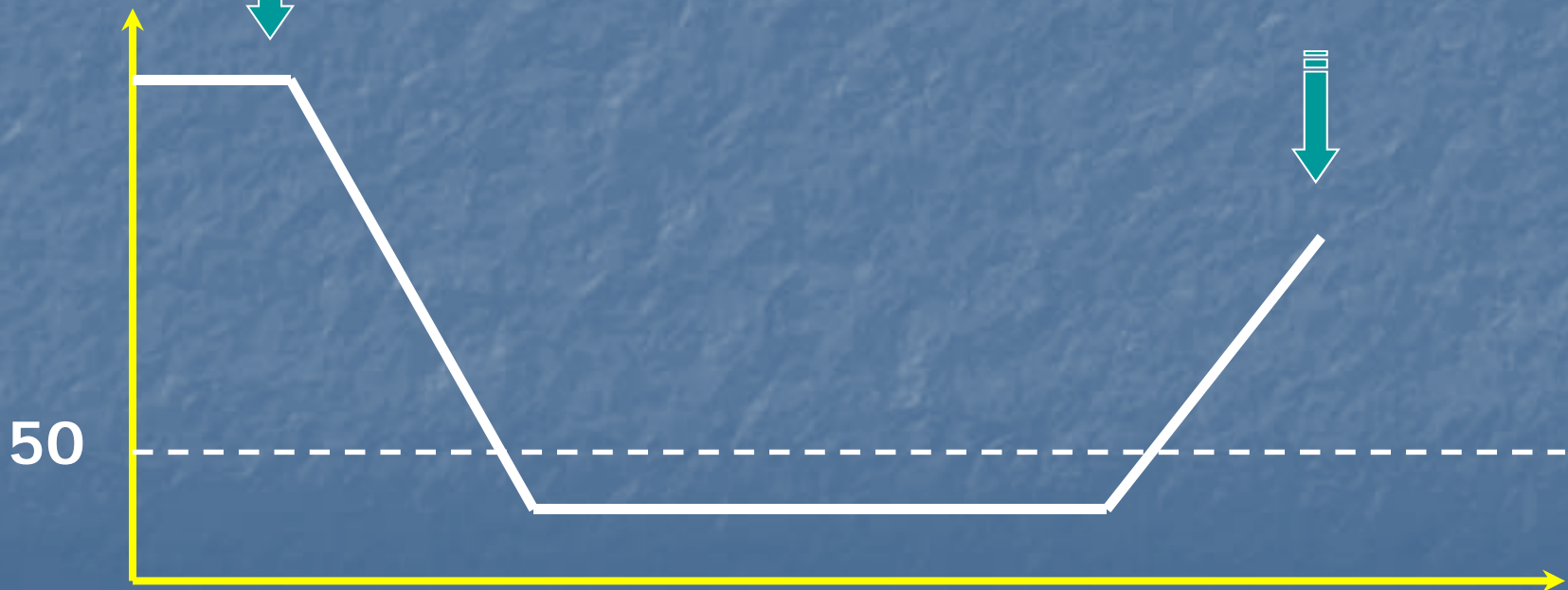
X, Y, Z



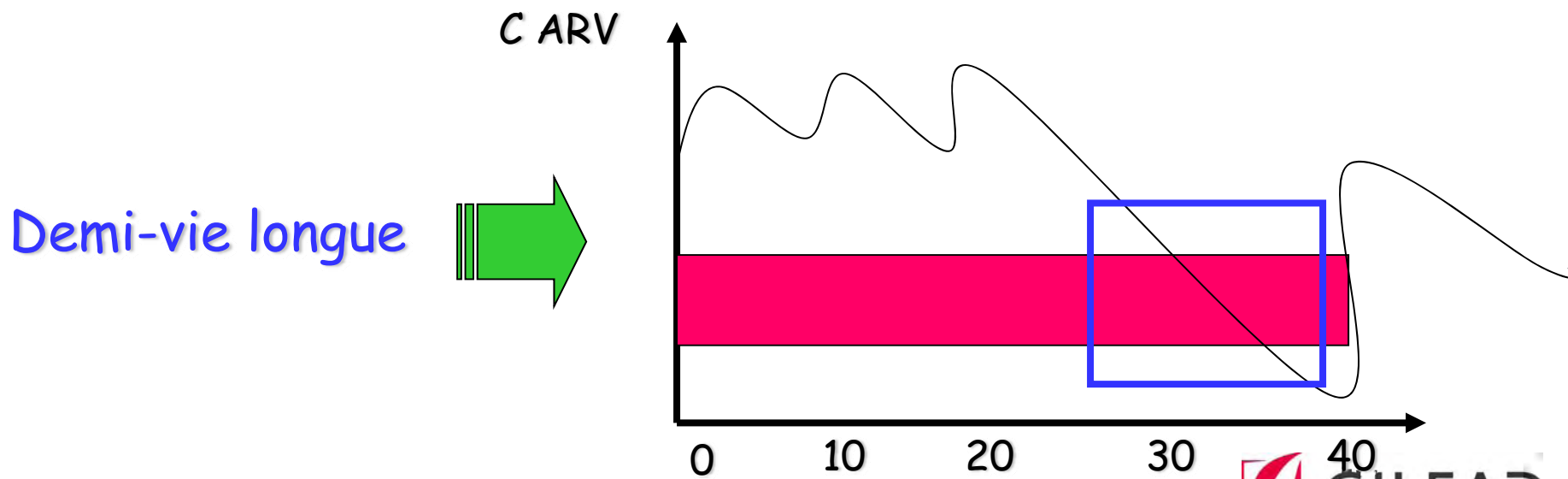
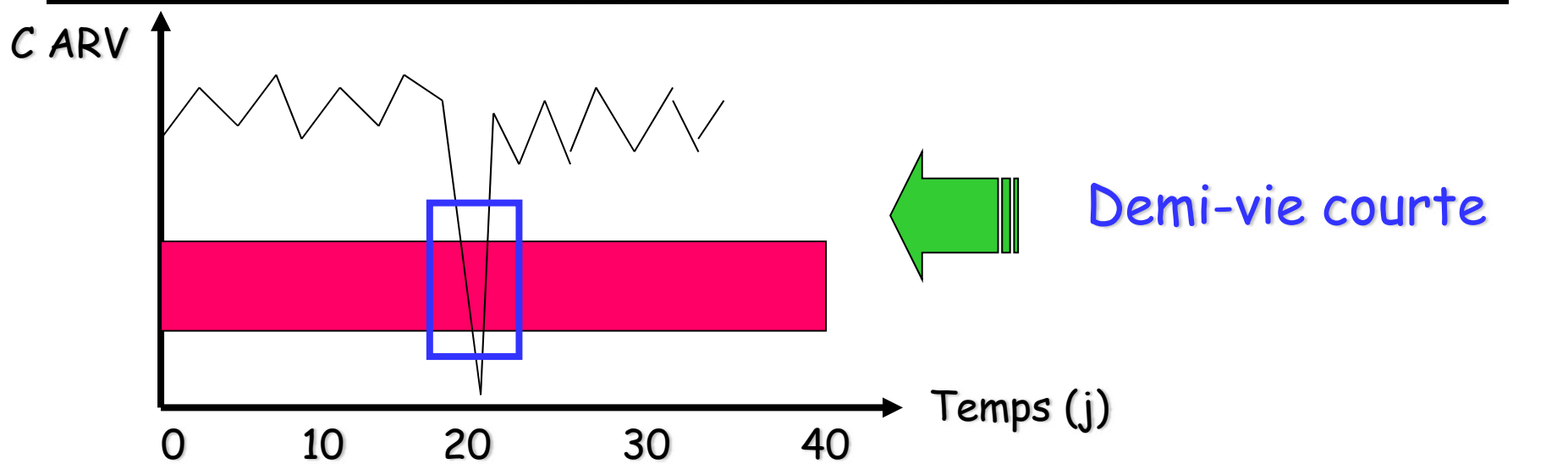
X, Y, Z

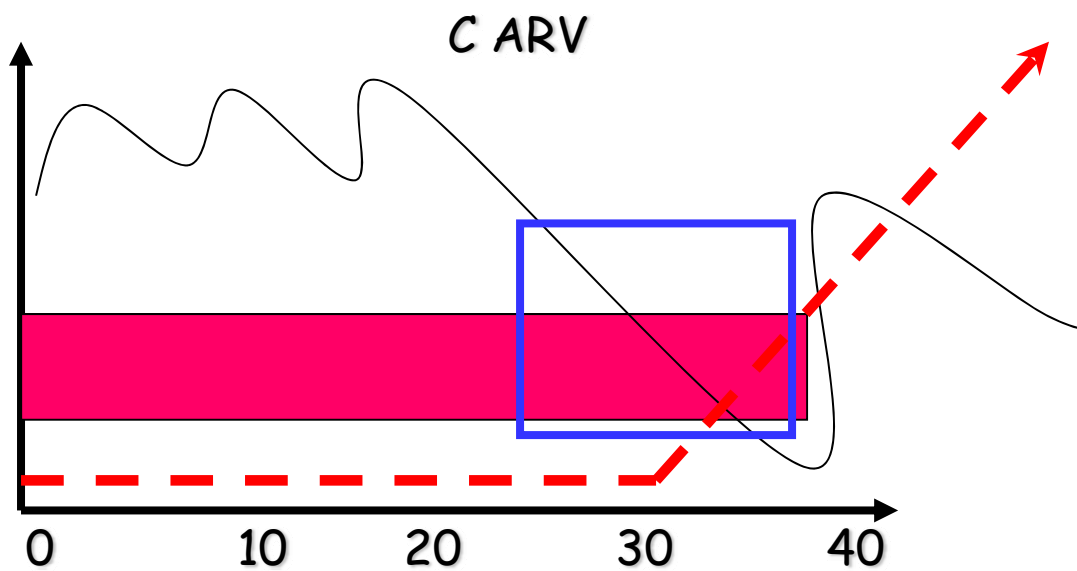
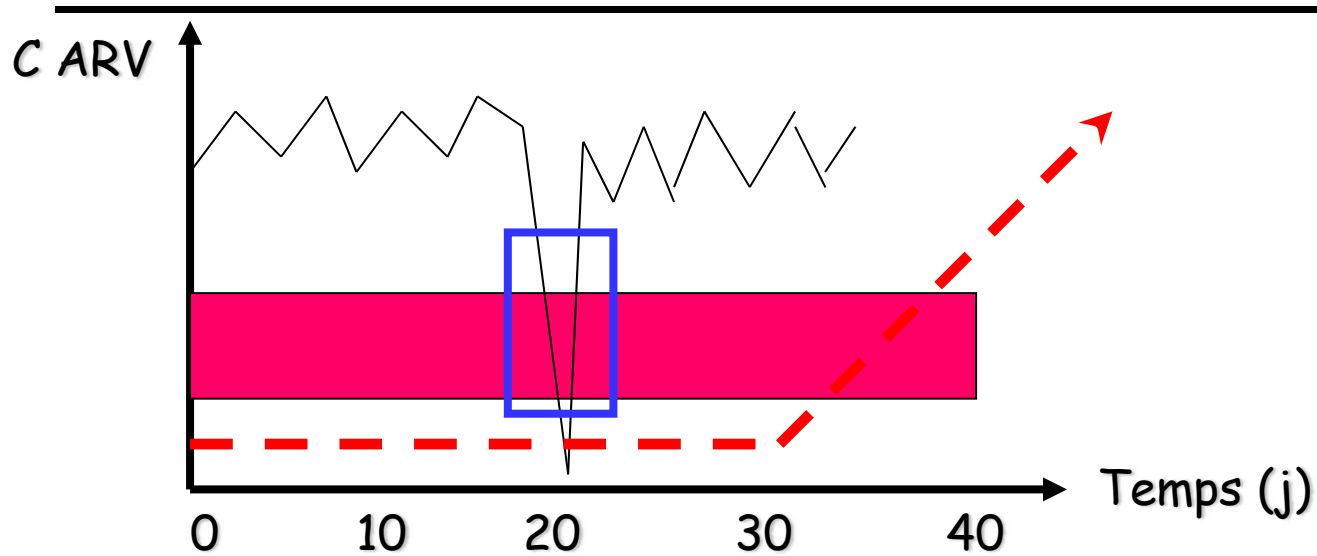


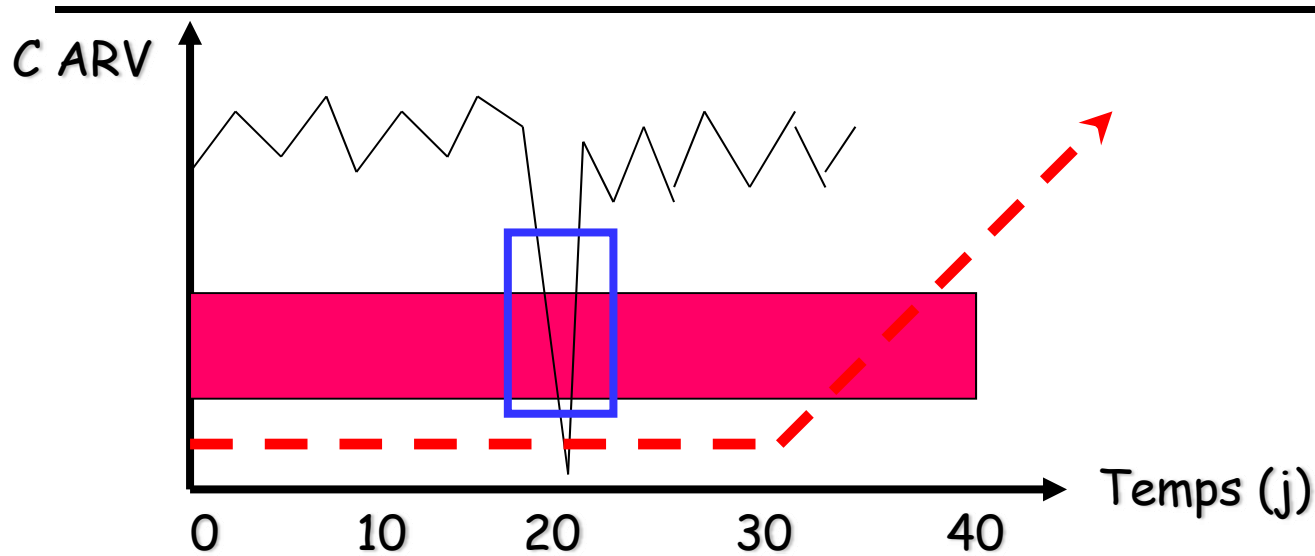
X, Y, Z



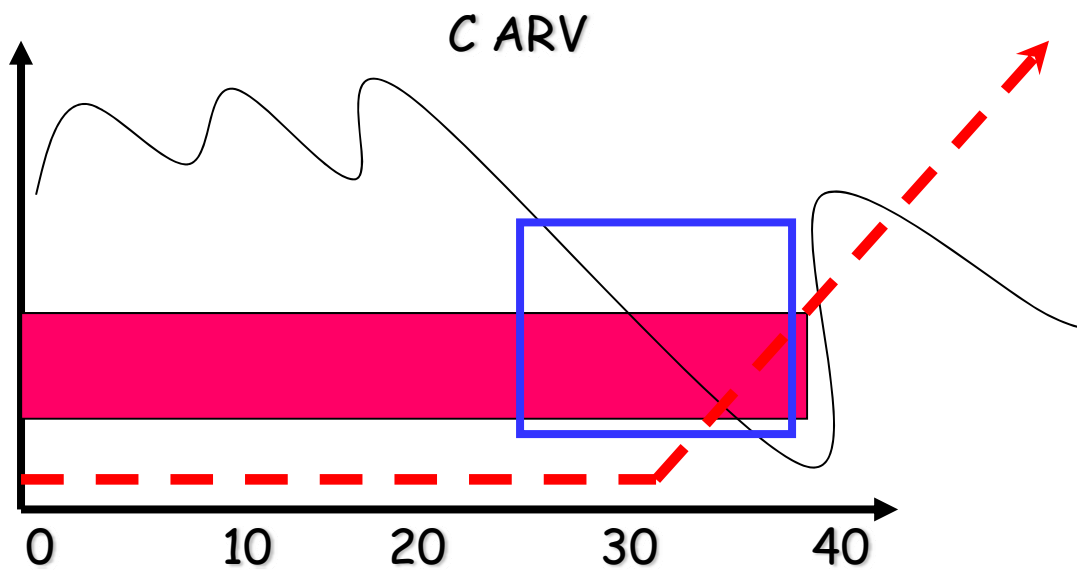
Impact de la $T_{\frac{1}{2}}$ sur les conséquences d'une non observance



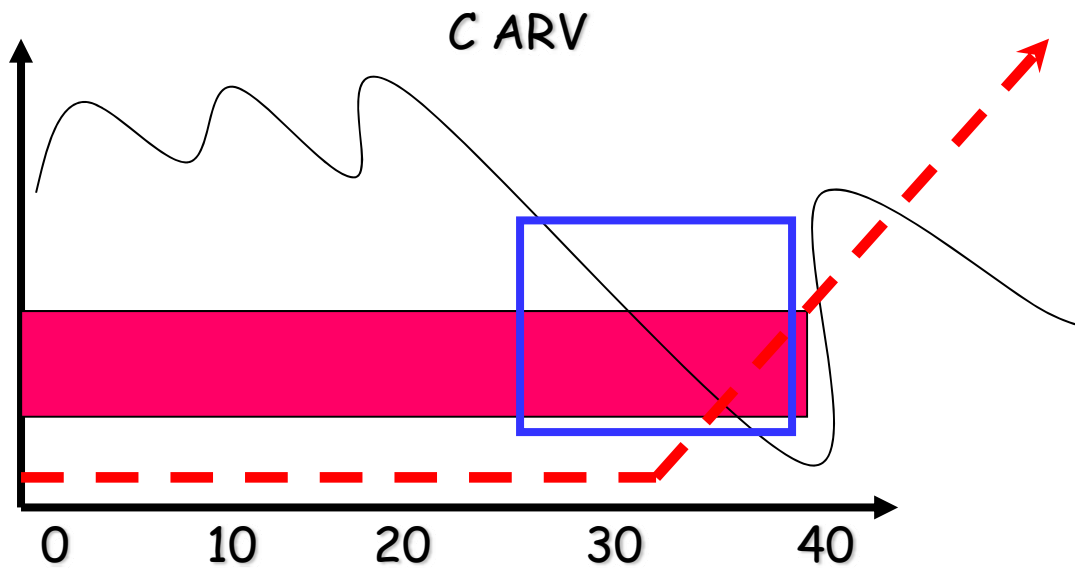
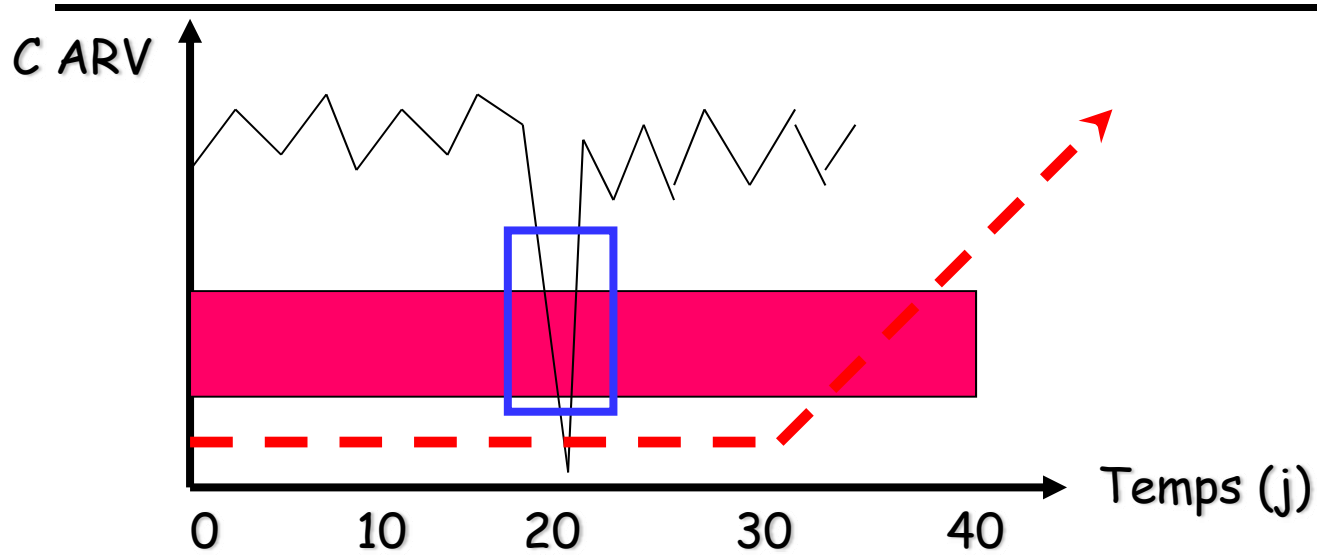




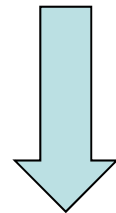
SEQUENCE



$$R = M \times E \times PS$$

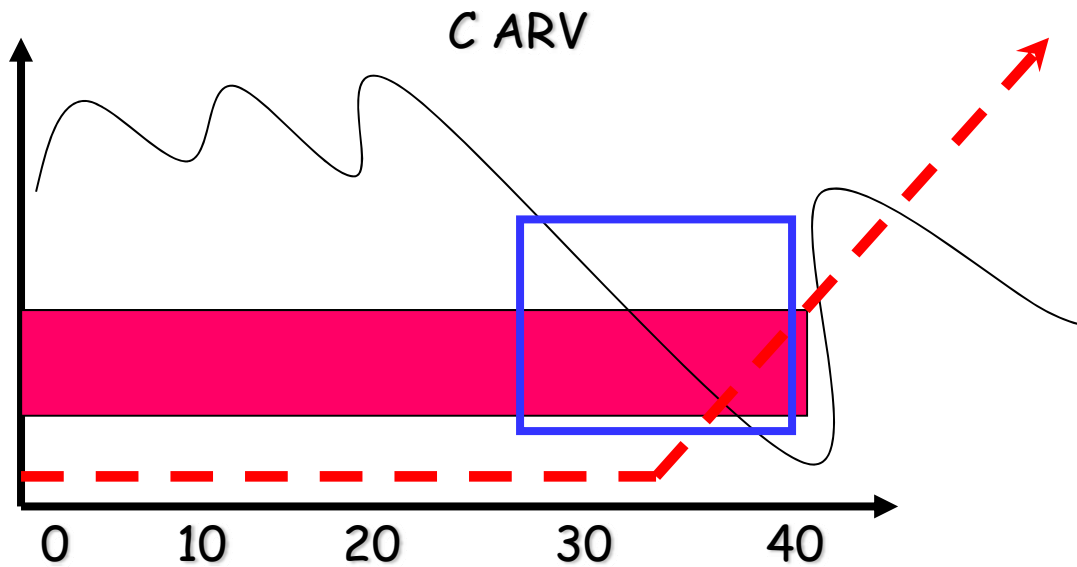
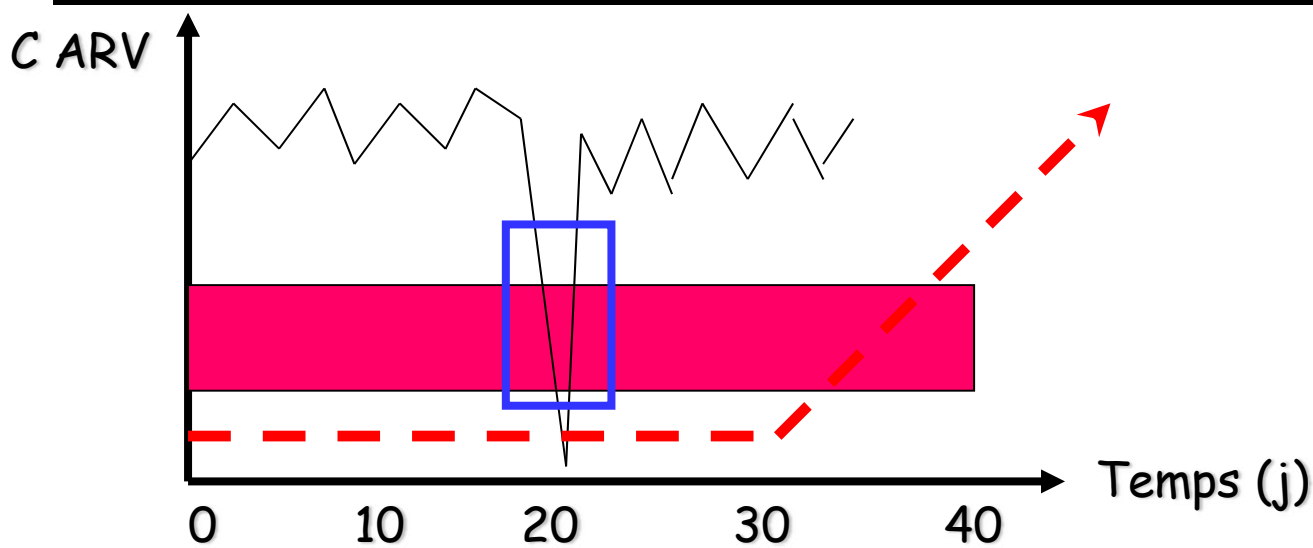


SEQUENCE



MUTATIONS

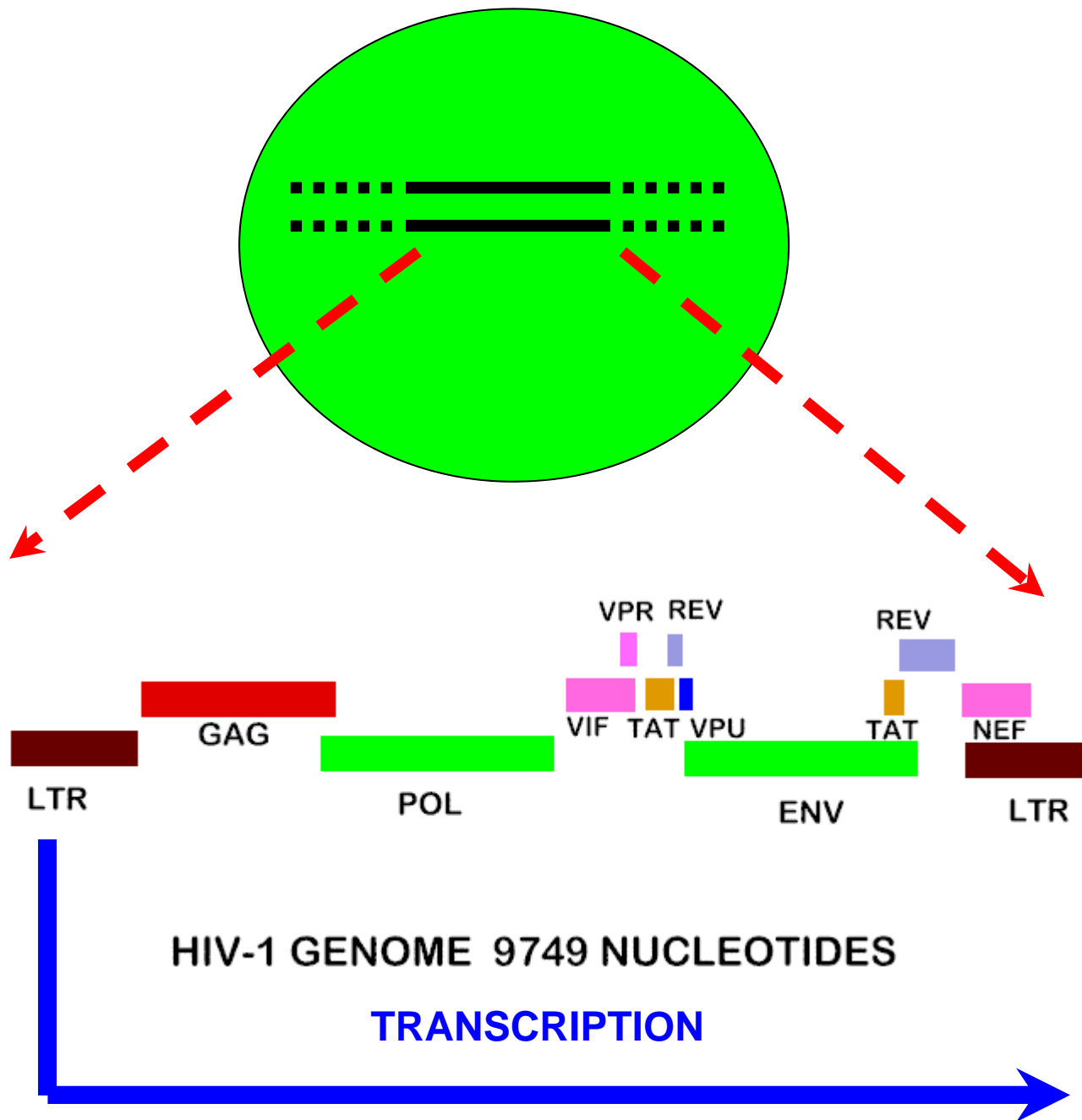
$$R = M \times E \times PS \quad (PS \approx 0)$$



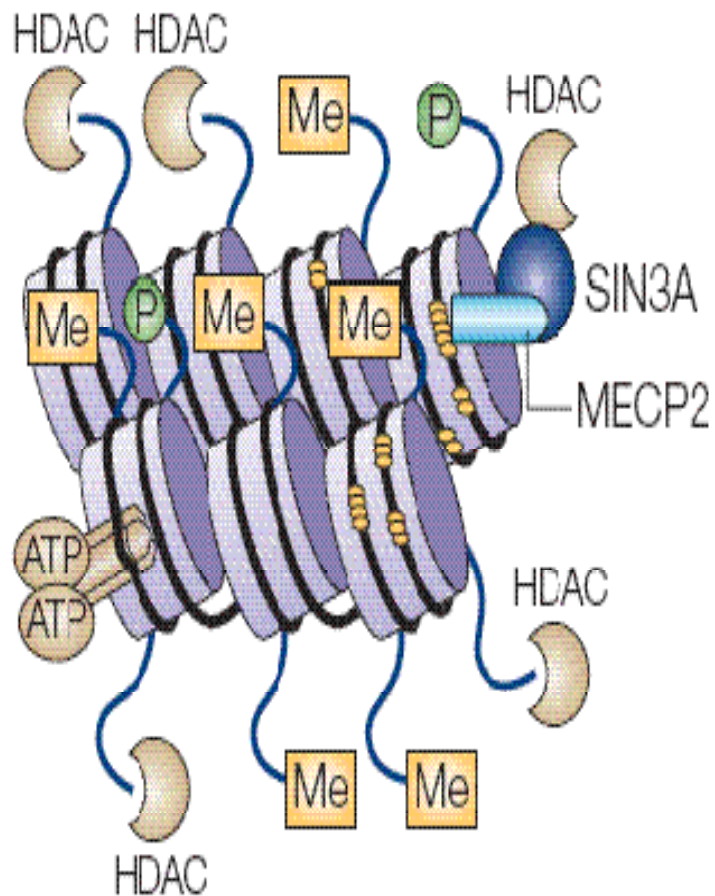
SAUVAGE

SEQUENCE

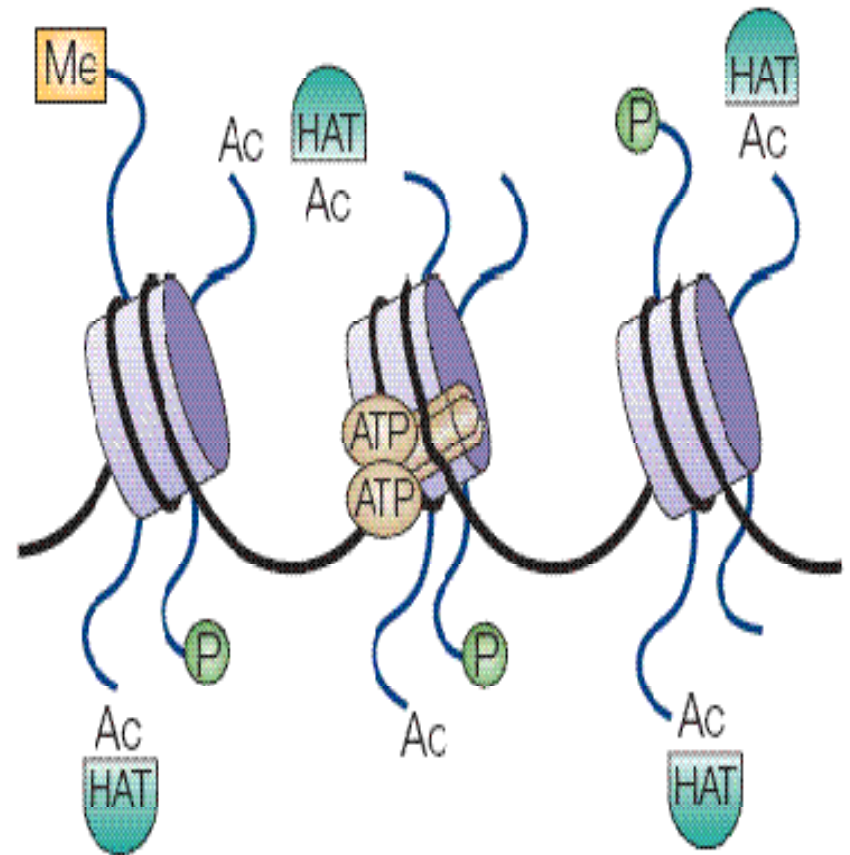
MUTATIONS



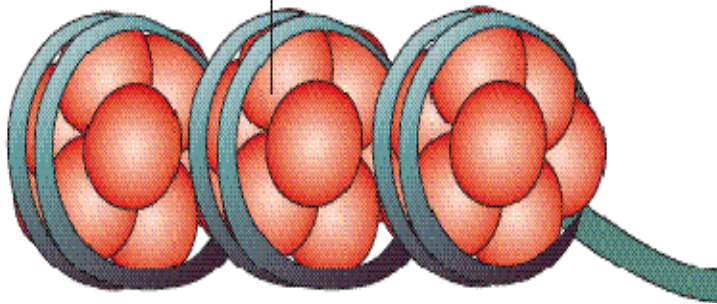
a Closed chromatin: transcriptional repression



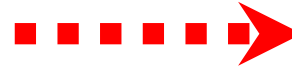
b Open chromatin: transcriptional activation



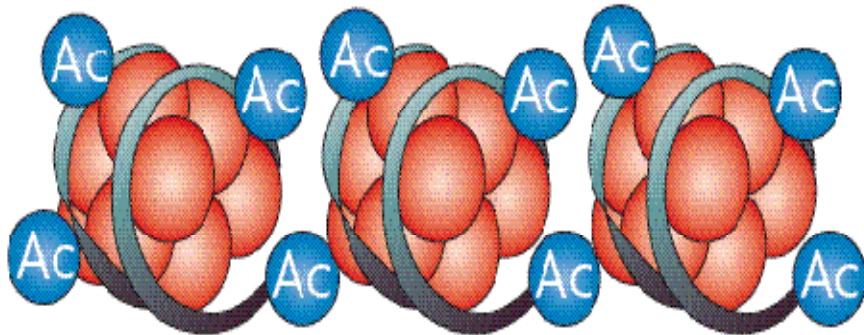
Nucleosomes



Inaccessible chromatin



Transcriptionally
silenced

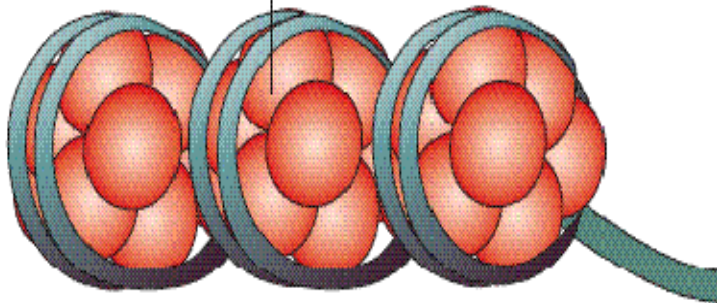


Open chromatin

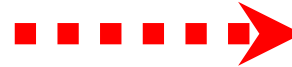


Gene
expression

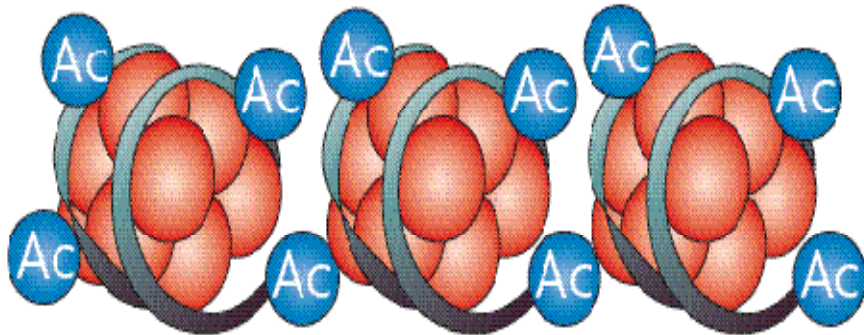
Nucleosomes



Inaccessible chromatin



Transcriptionally
silenced

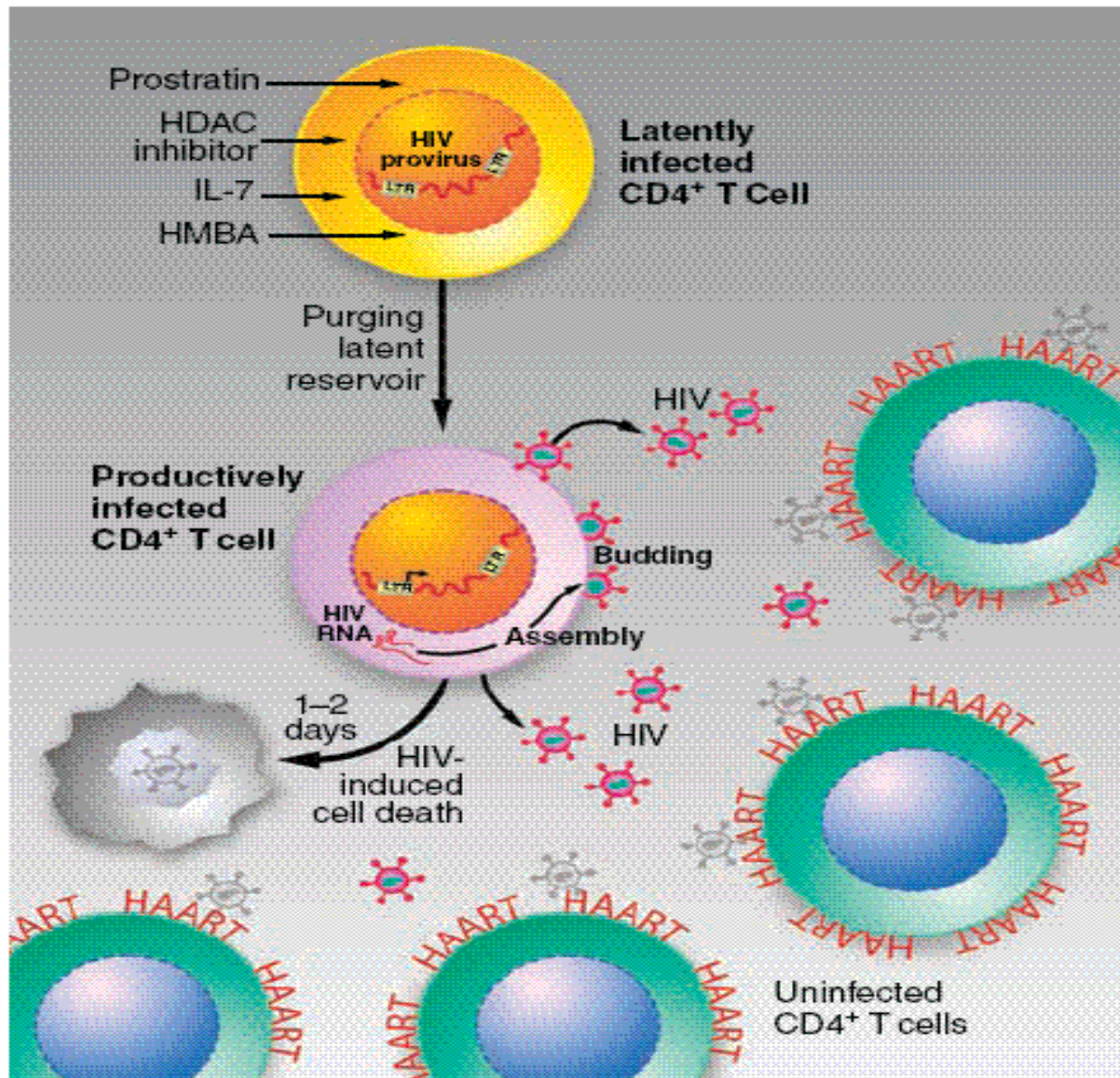


Open chromatin



Gene
expression

HDAC inhibitors
Hyperacetylation of histones
VALPROIC ACID



CONCLUSION

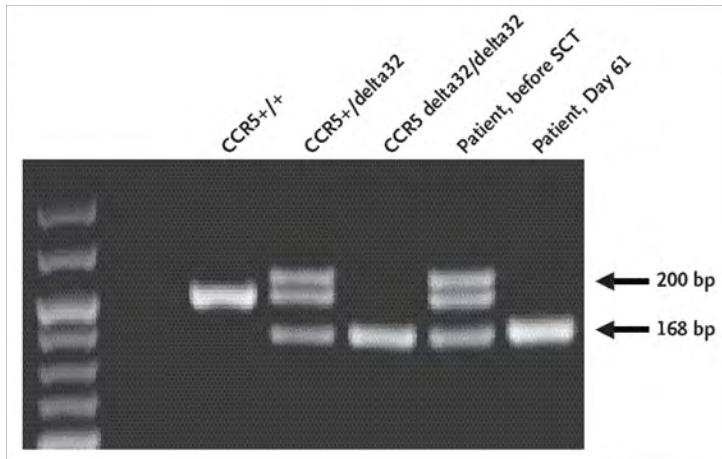
« The eradication of HIV-1 infection cannot be achieved by intensification of therapy.

All the stable reservoirs must be identified.

Before this goal is achieved , we can at least offer patients the reassurance that modern HAART regimens, if taken correctly, can maintain suppression of viral replication **indefinitely**. »

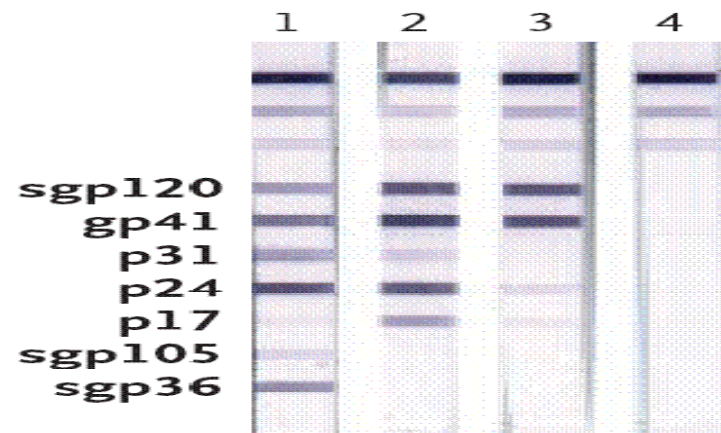
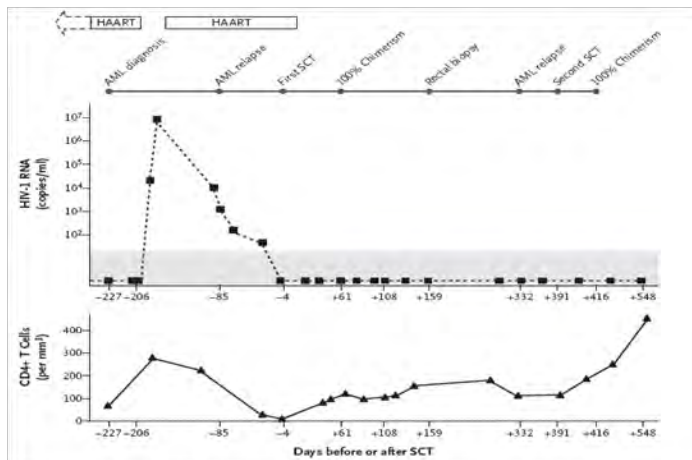
Long-Term Control of HIV by CCR5 Delta32/ Delta32 Stem-Cell Transplantation

G.Hutter et al ; NEJM 2009 ; 360 : 692-8



ANALYSIS OF HIV-1 CORECEPTOR PHENOTYPE

Sequence analysis of the patient's viral variants revealed a glycine at position 11 and a glutamic acid at position 25 of the V3 region. The net charge of amino acids was +3. These results indicated CCR5 coreceptor use by the HIV-1 strain infecting the patient, a finding that was confirmed by sequencing RNA in the HIV *env* region. The ultradeep sequencing analysis revealed a proportion of 2.9% for the X4 and dual-tropic variants combined.



Evidence for the cure of HIV infection by CCR5{Delta}32/{Delta}32 stem cell transplantation

K.Allers et al ; Blood 2011, in press

In summary, our results demonstrate successful CD4⁺ T cell reconstitution at the systemic level as well as in the largest immunologic organ following CCR5 Δ 32/ Δ 32 SCT, and additionally provide evidence for the reduction in the size of the potential HIV reservoir over time. Although the recovered CD4⁺ T cells are susceptible to infection with X4 HIV infection, the patient remains without any evidence for HIV infection since more than 3.5 years after discontinuation of ART. From these results, it is reasonable to conclude that cure of HIV infection has been achieved in this patient.

LES FEMMES FÊTENT LE 8 MARS

