

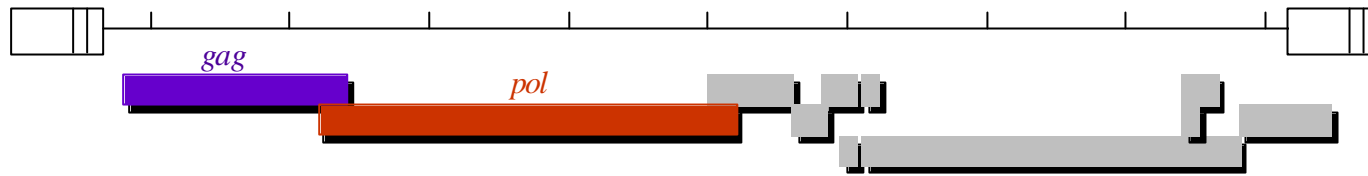
# **HIV drug resistance : resistance, fitness and diversity**

**François Clavel  
Inserm U552  
Université Paris 7 Denis Diderot**

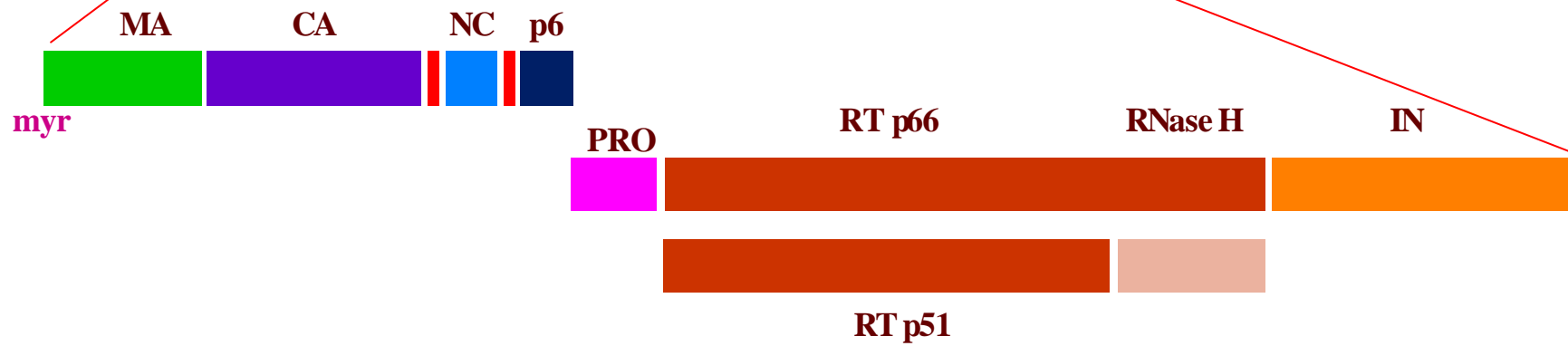
## **To escape treatment, HIV must :**

- Decrease drug susceptibility
- Preserve fitness
- Preserve diversity

# **Resistance et fitness**

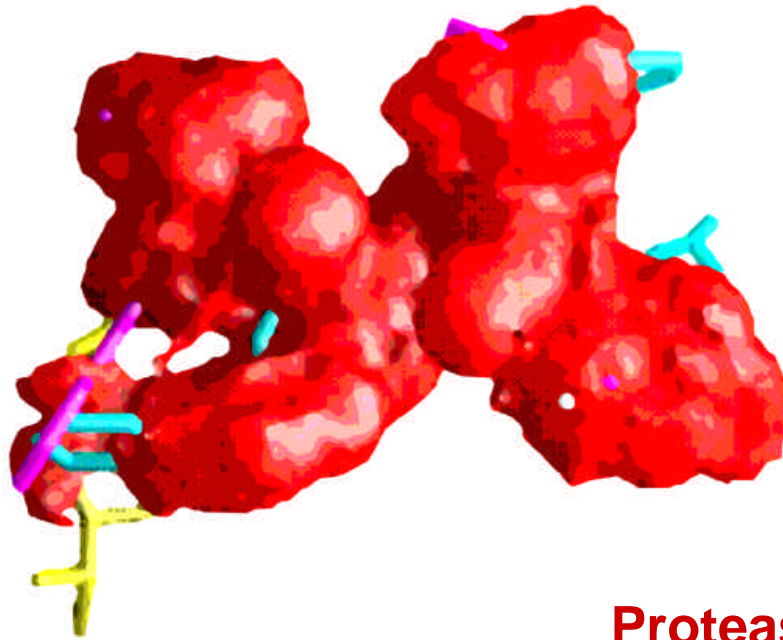
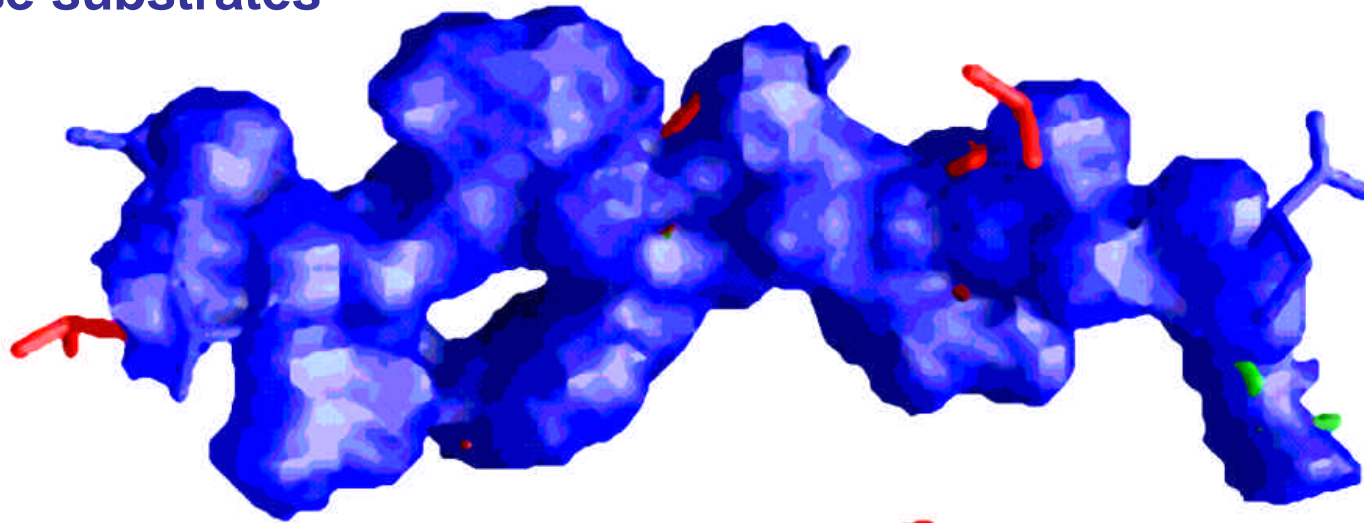


9,2 kb : gag, pol

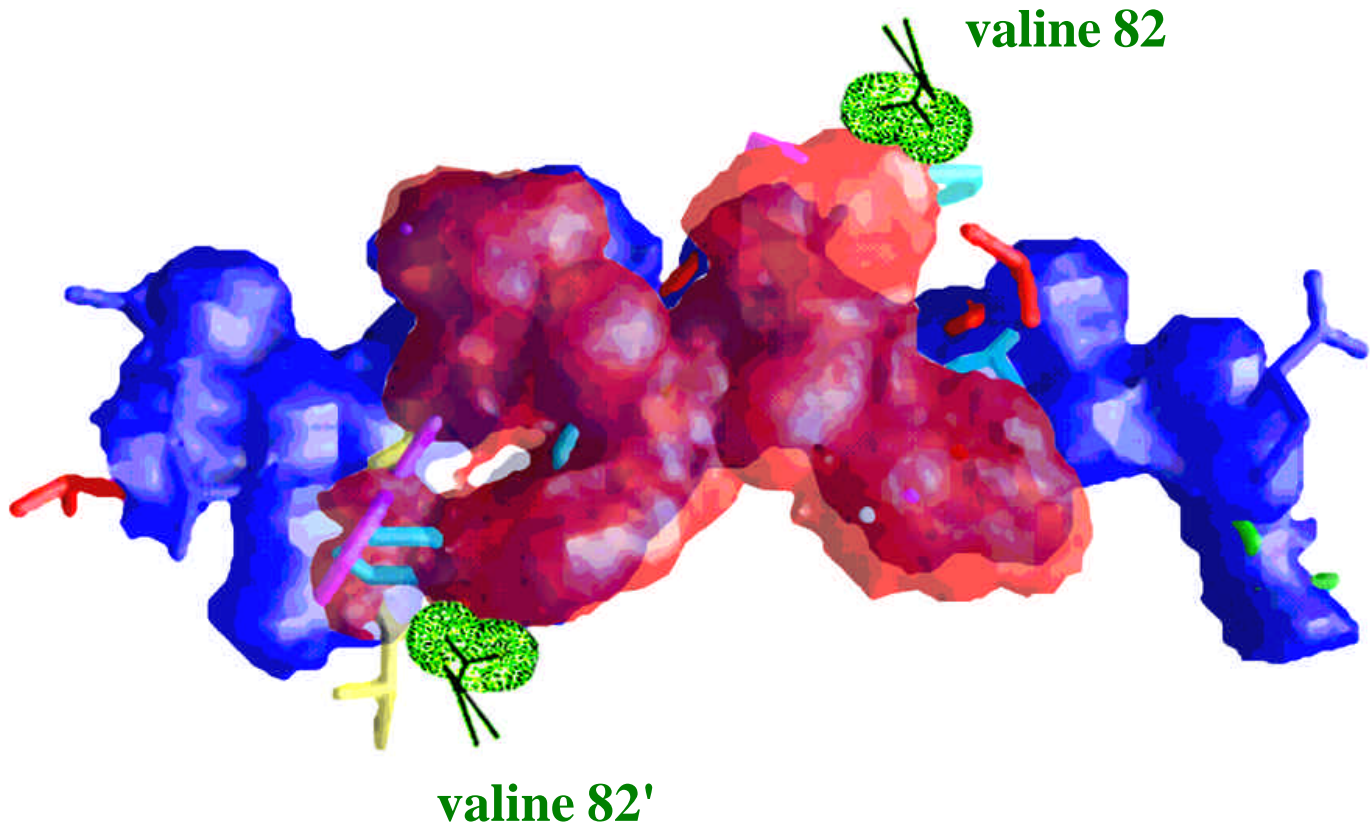


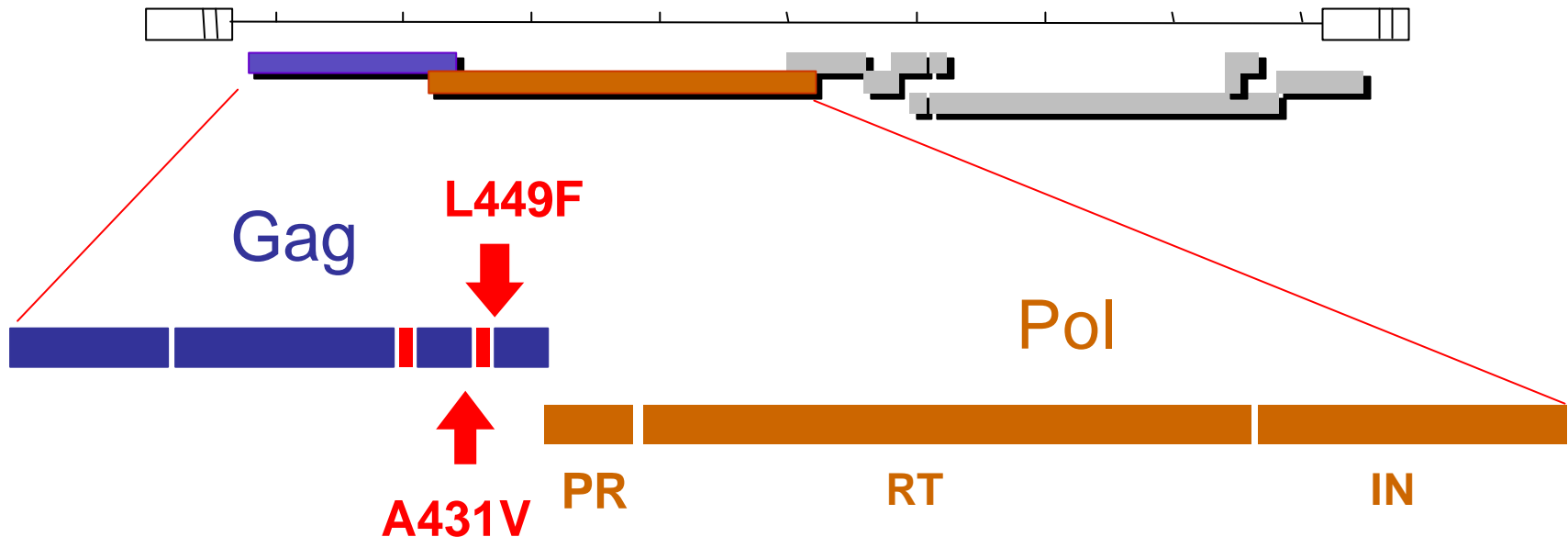


## Protease substrates

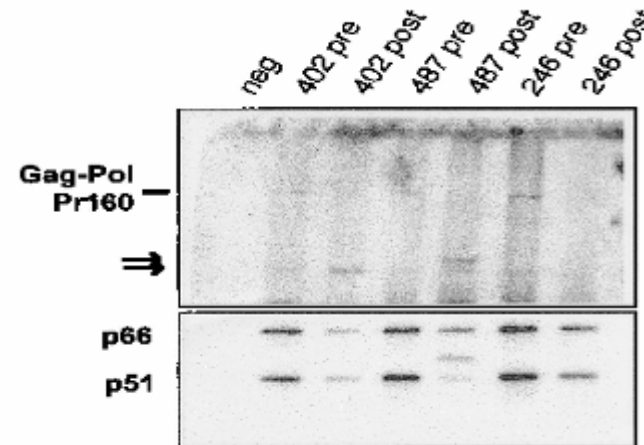
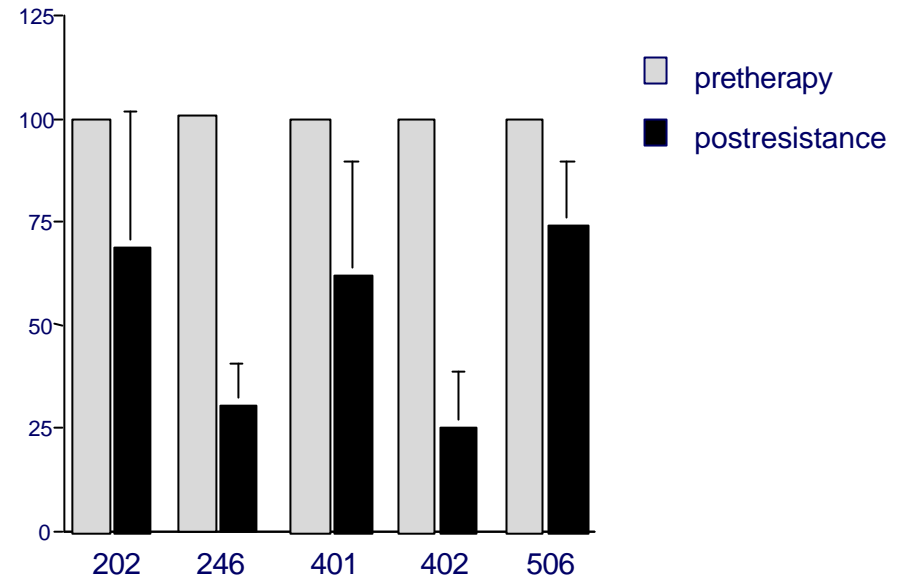
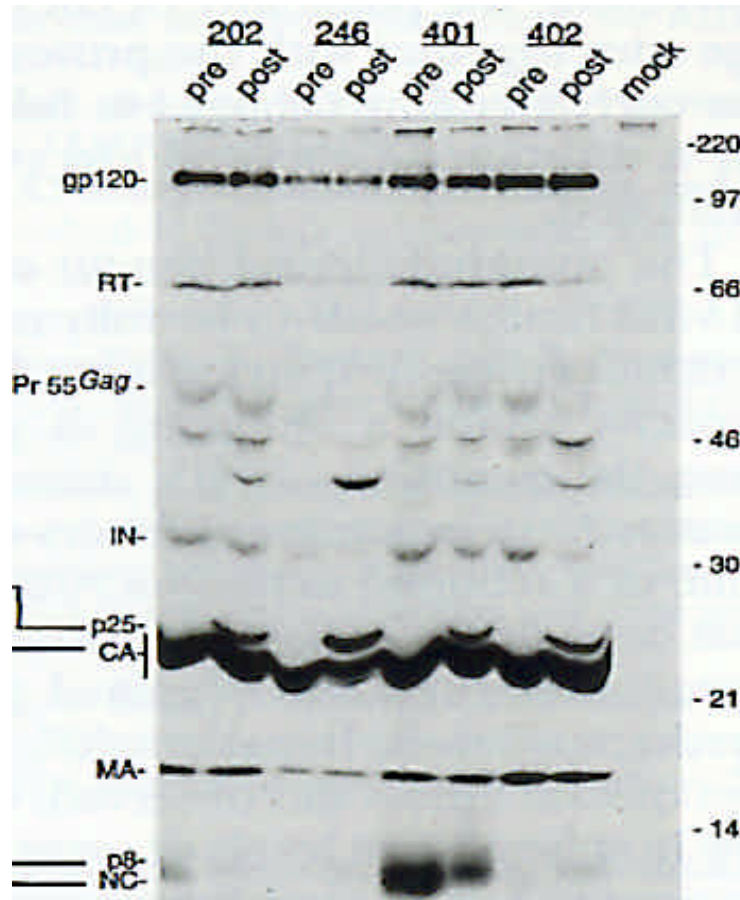


## Protease inhibitors

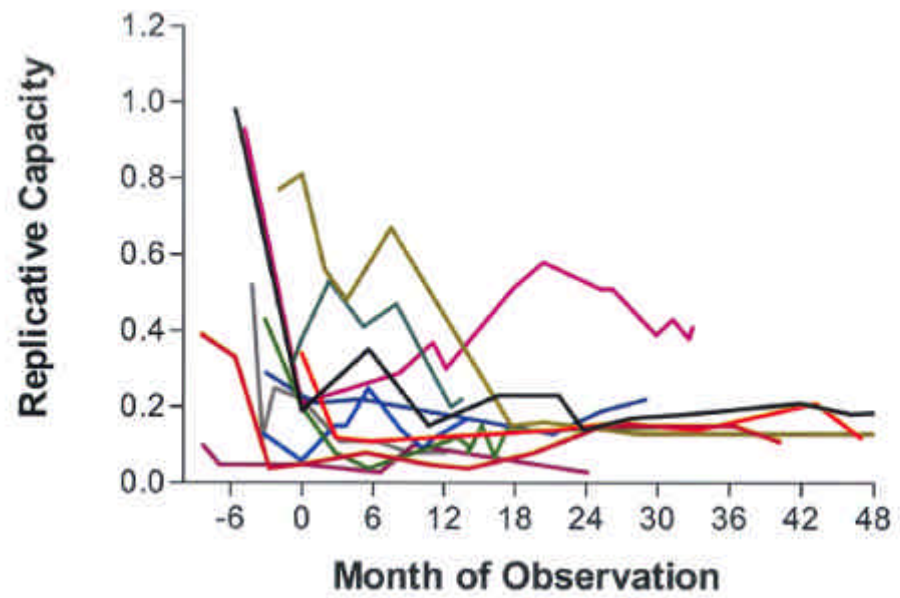
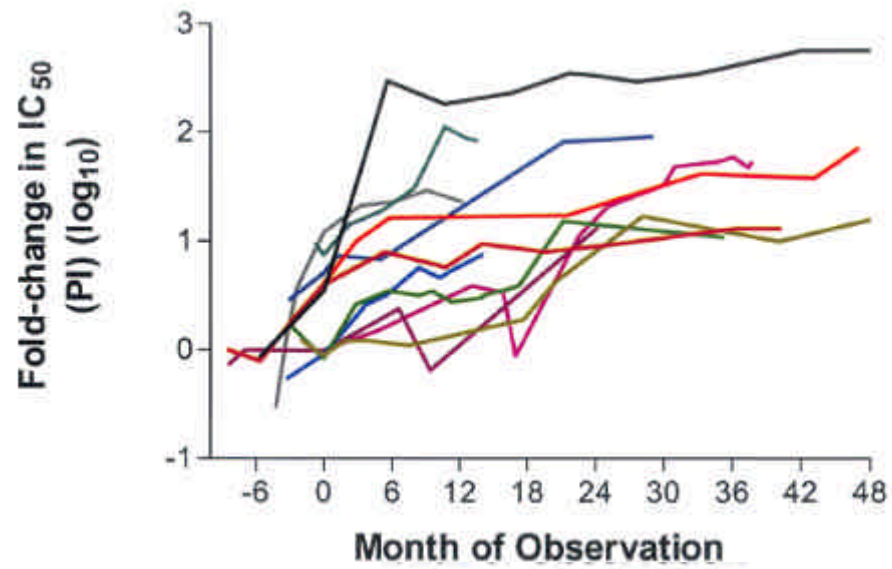




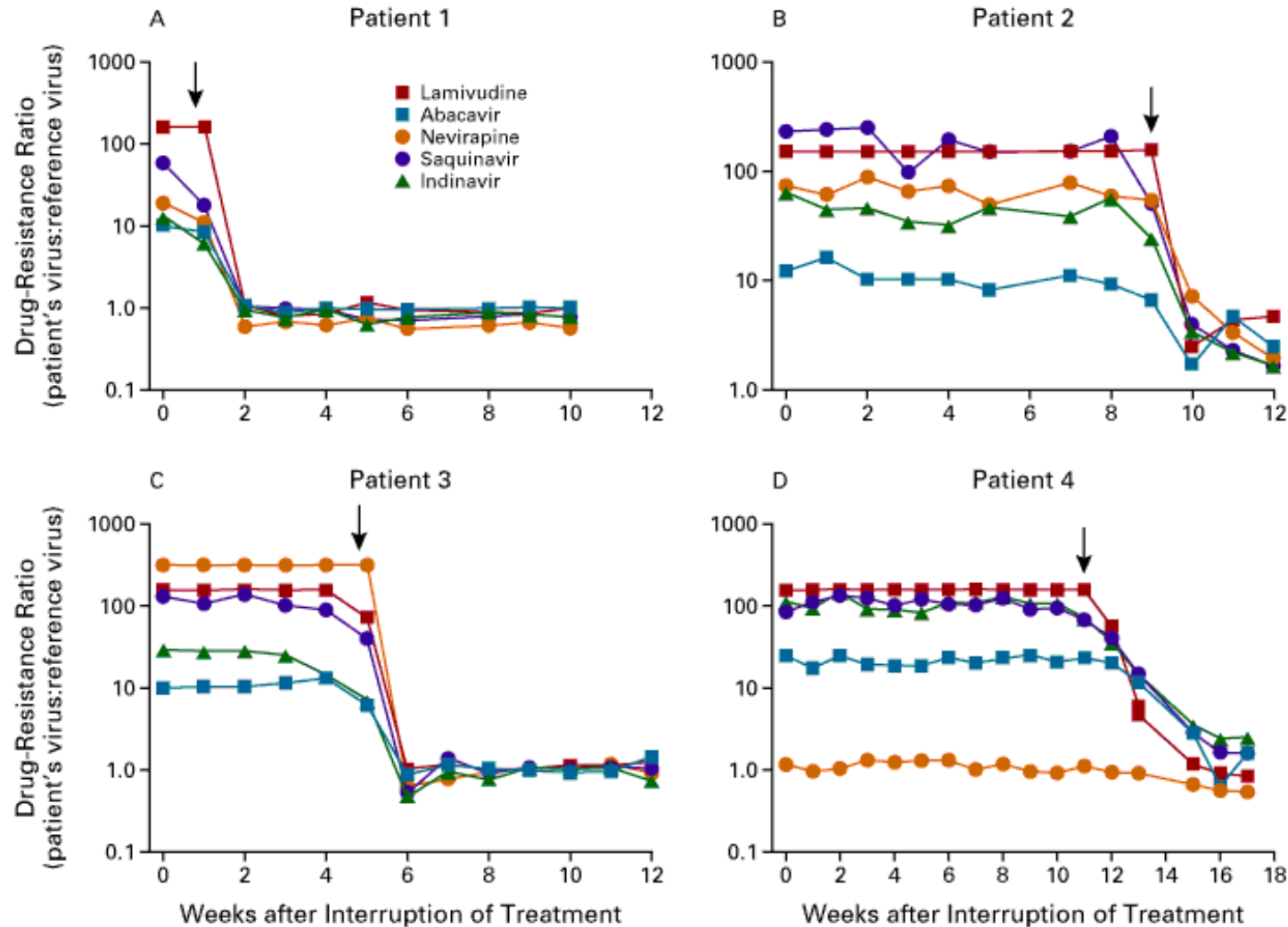
# Resistance and PR function



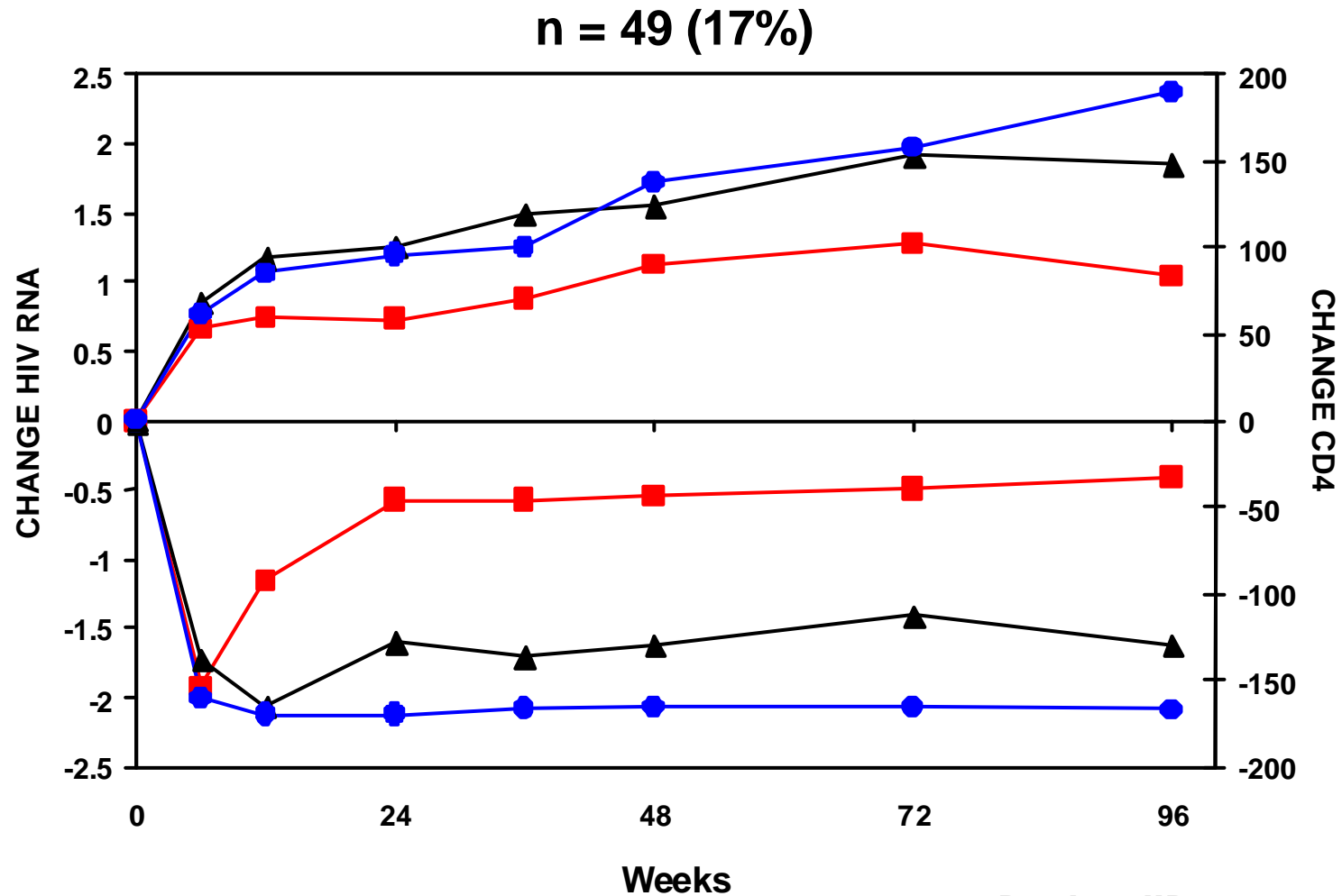
V. Zennou et al.  
 F. Mammano et al.  
 L. Carron de la Carrière et al.



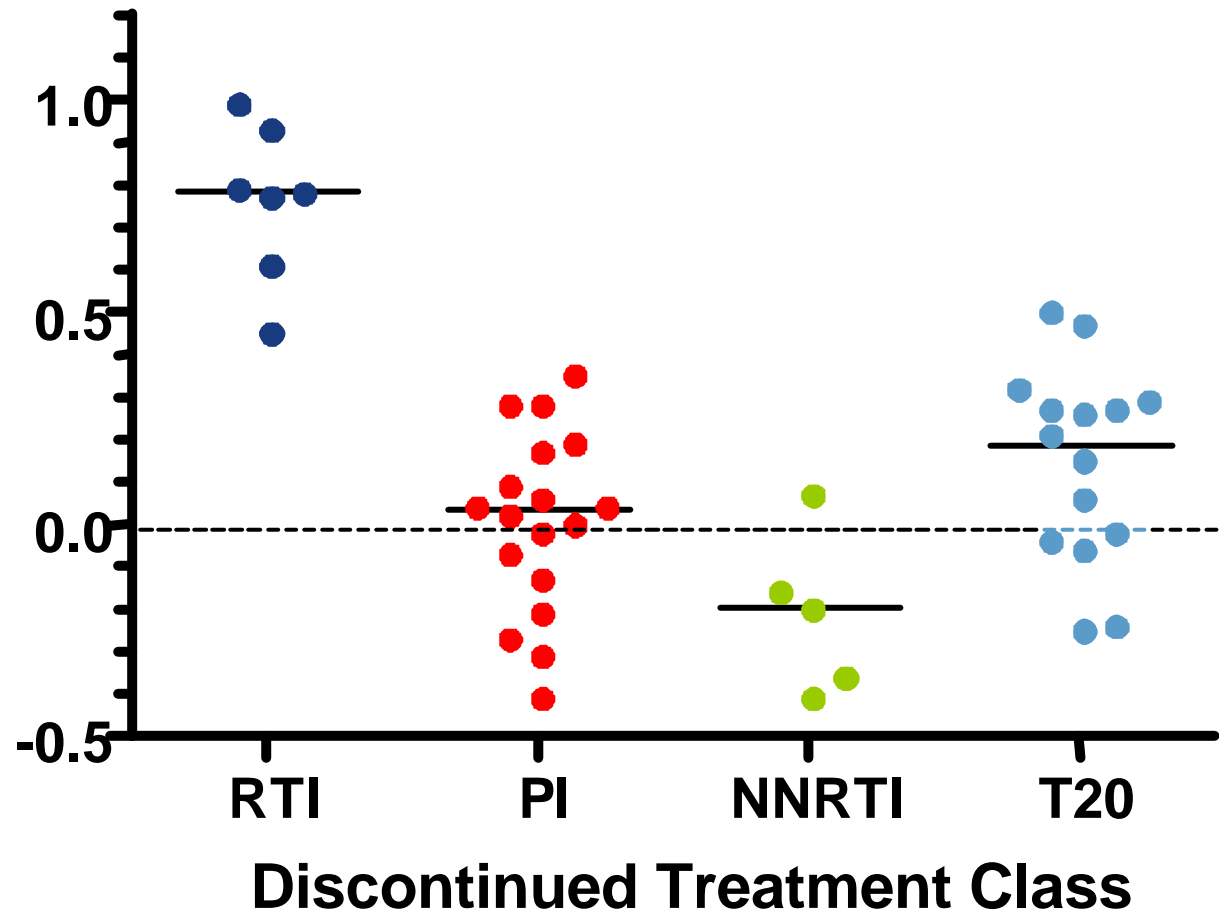
# Phenotypic switch after treatment interruption



# Even Transient Virologic Responses Are Associated with Increased CD4<sup>+</sup> T Cells



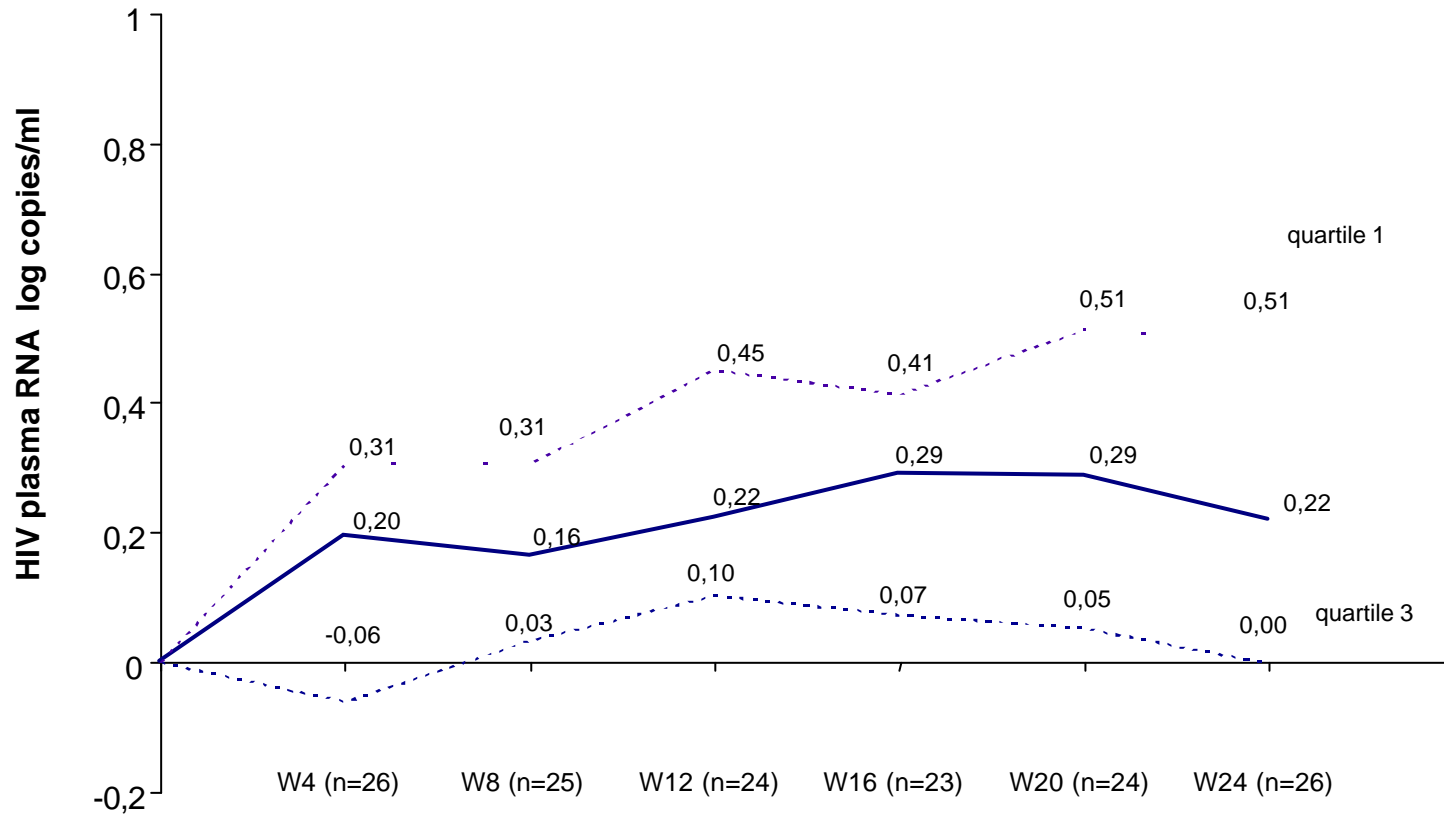
# Residual activity of NRTIs in vivo



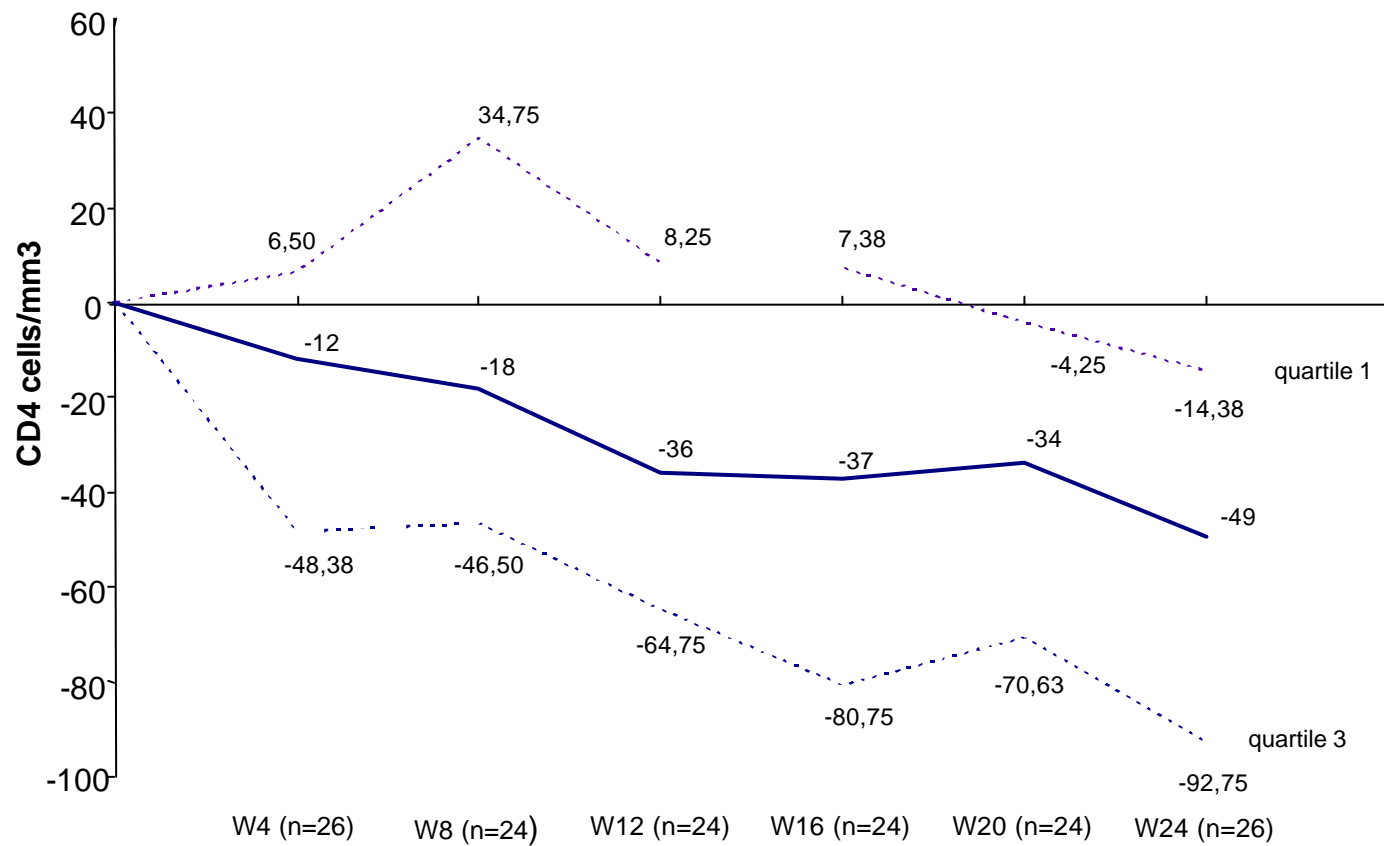
# ANRS109 "Vista" study

- 26 patients with multiple HAART failure and high-level triple class resistance
- CD4 >100/ $\mu$ l; VL < 10<sup>5</sup>/ml
- Replace failing HAART by low-dose IDV + 3TC to relieve residual HAART pressure and prevent resurgence of WT virus
- Measure Gag-PR fitness and correlate with CD4 changes

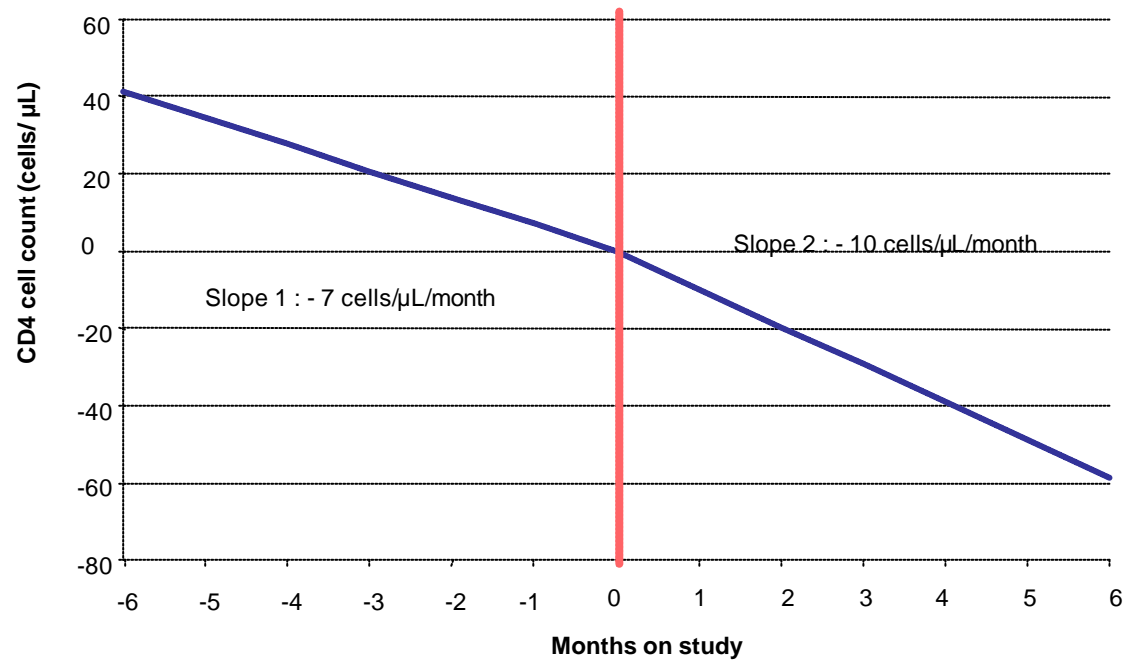
### Median change in plasma HIV RNA



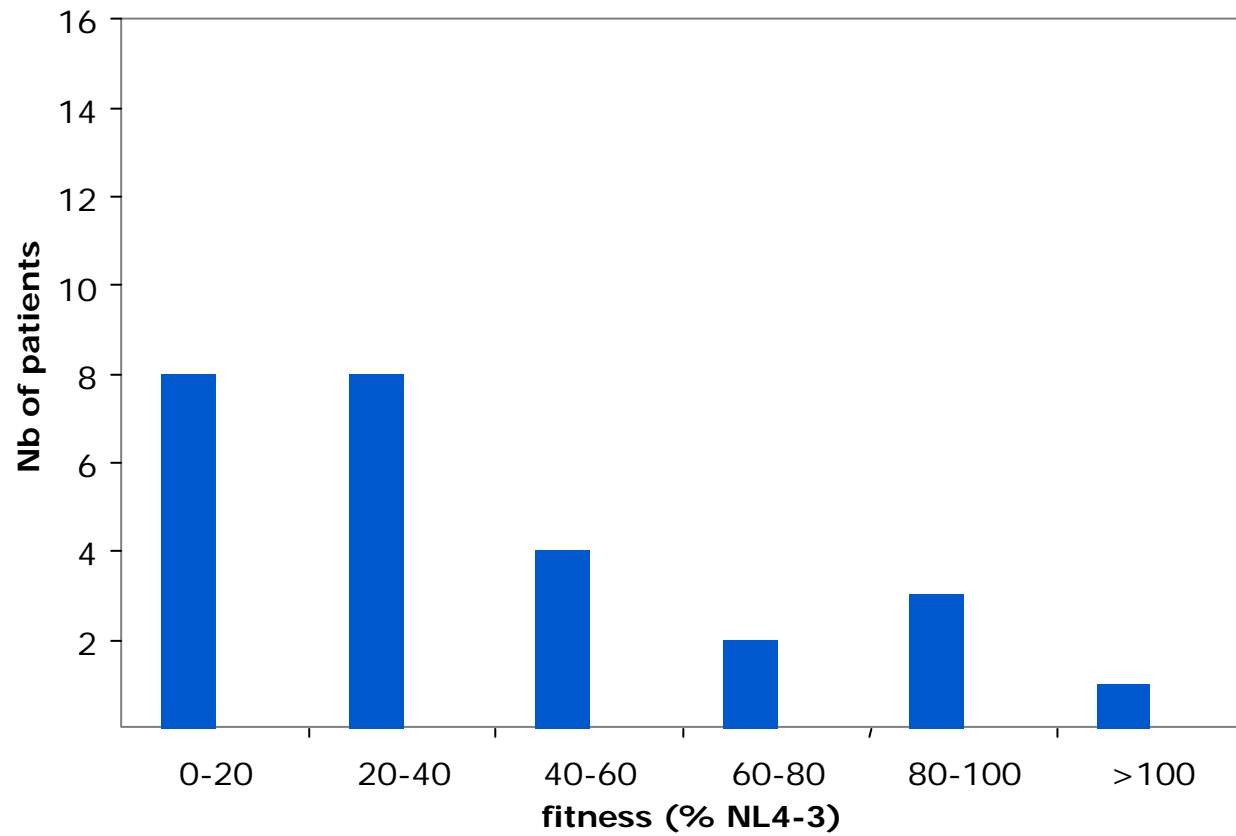
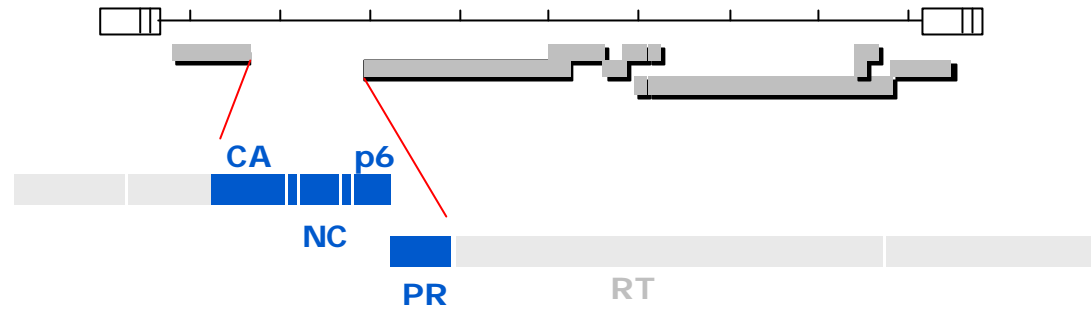
## Median change in CD4 counts



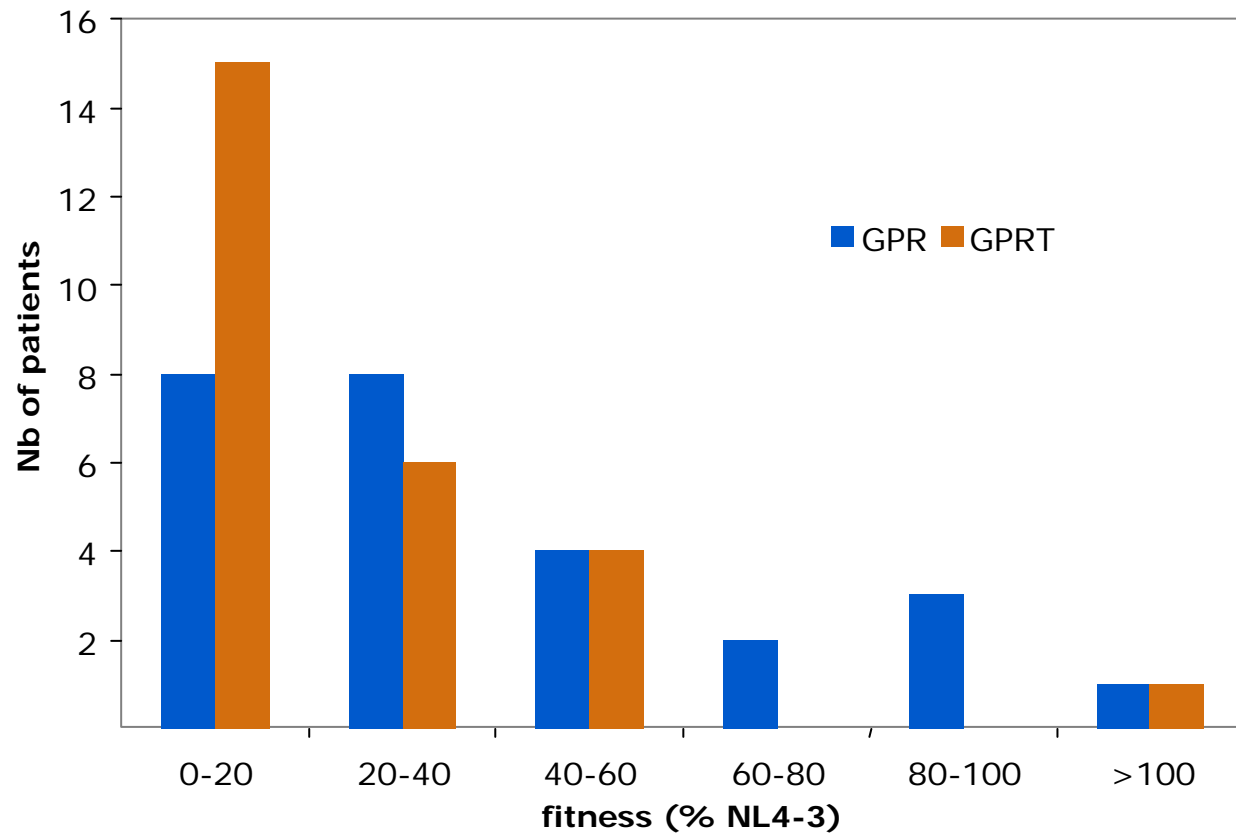
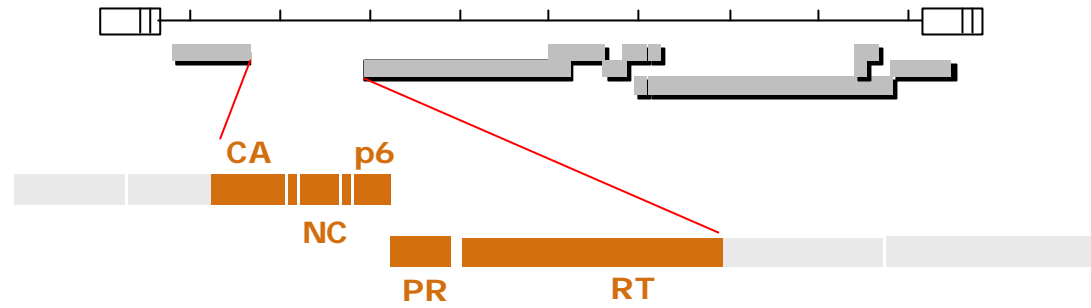
## CD4 slopes



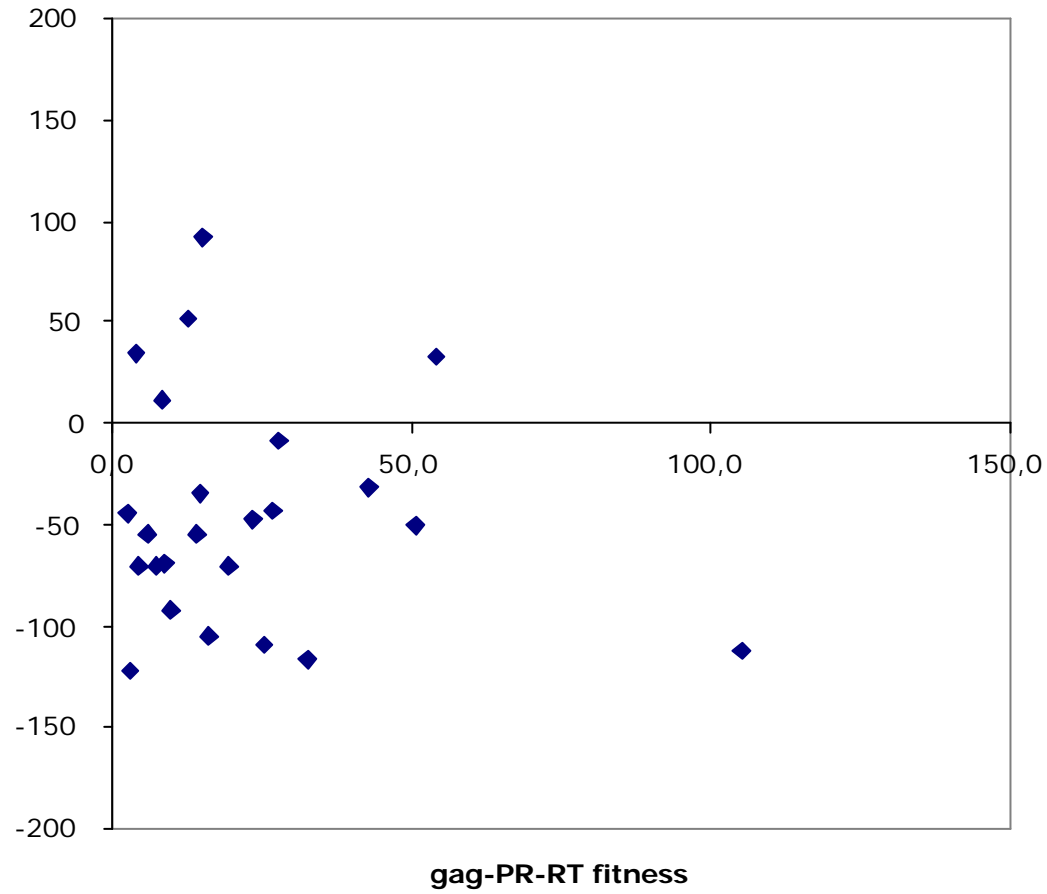
# Gag-PR fitness



# Gag-PR-RT fitness

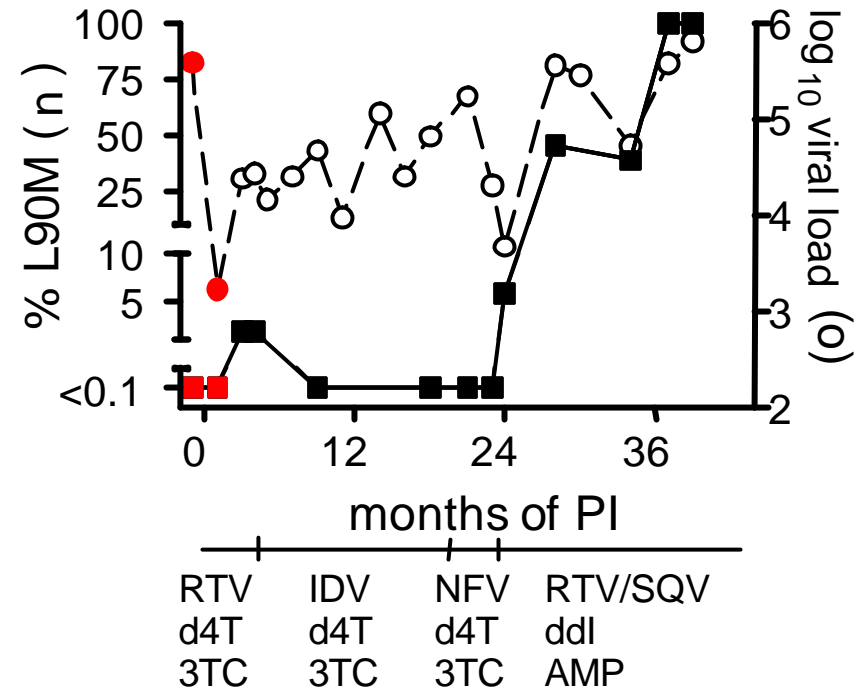
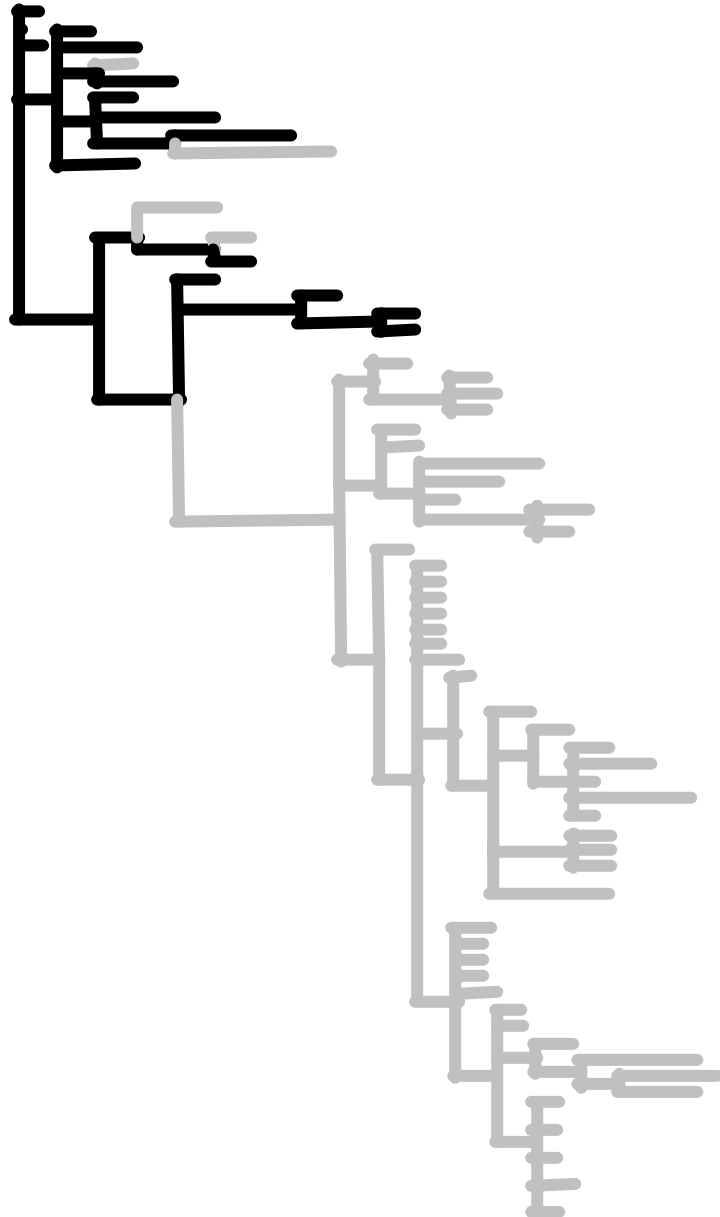


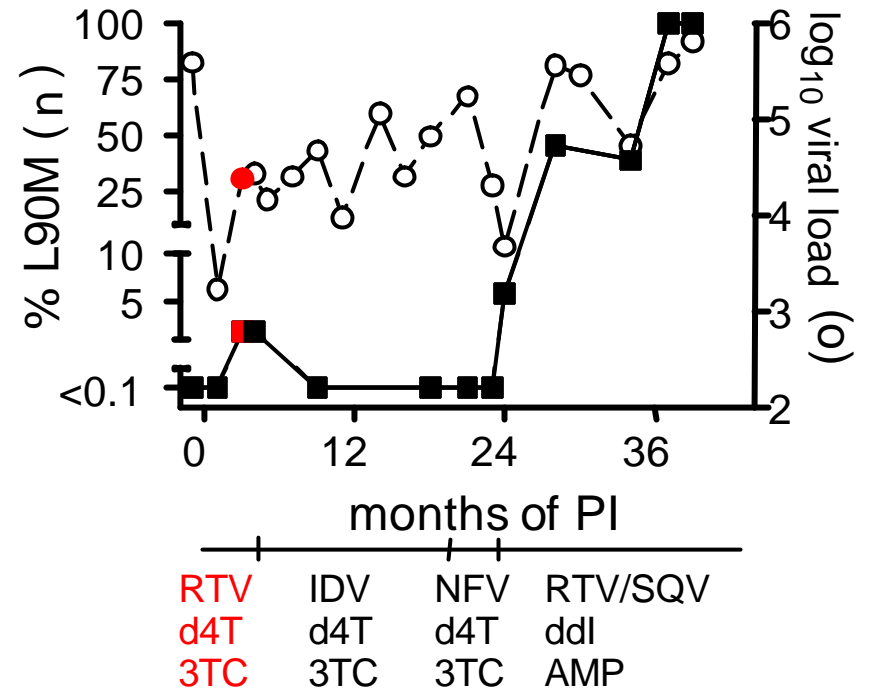
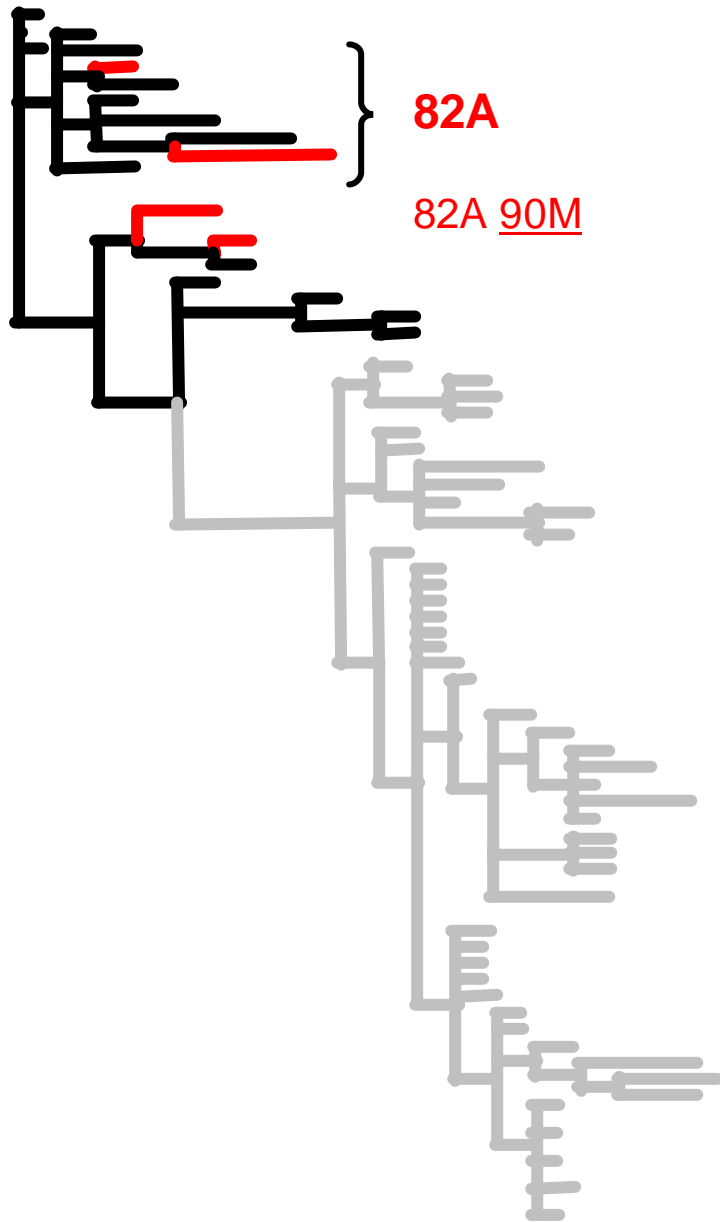
# Low viral fitness does not prevent CD4 loss

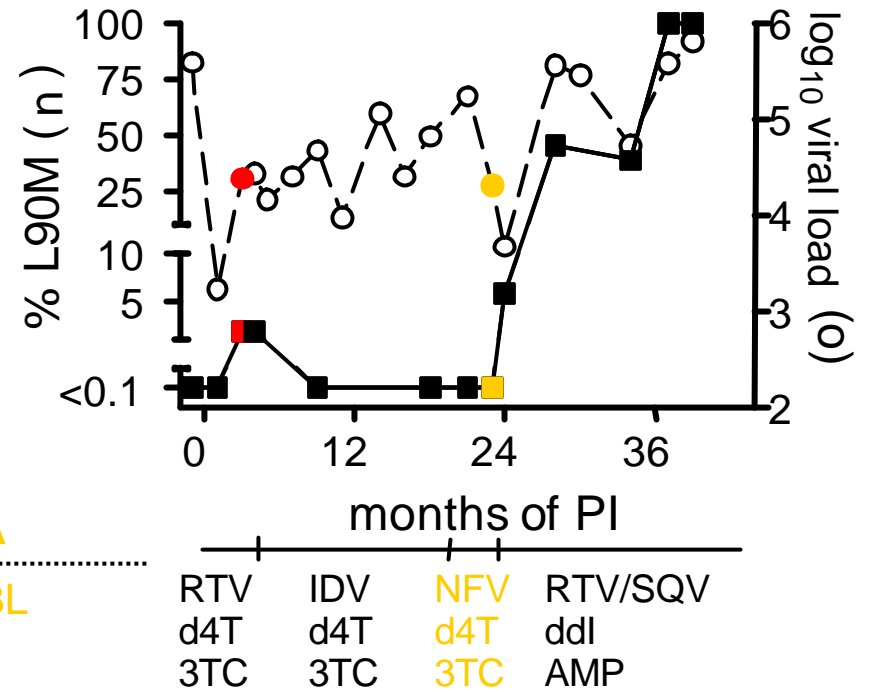
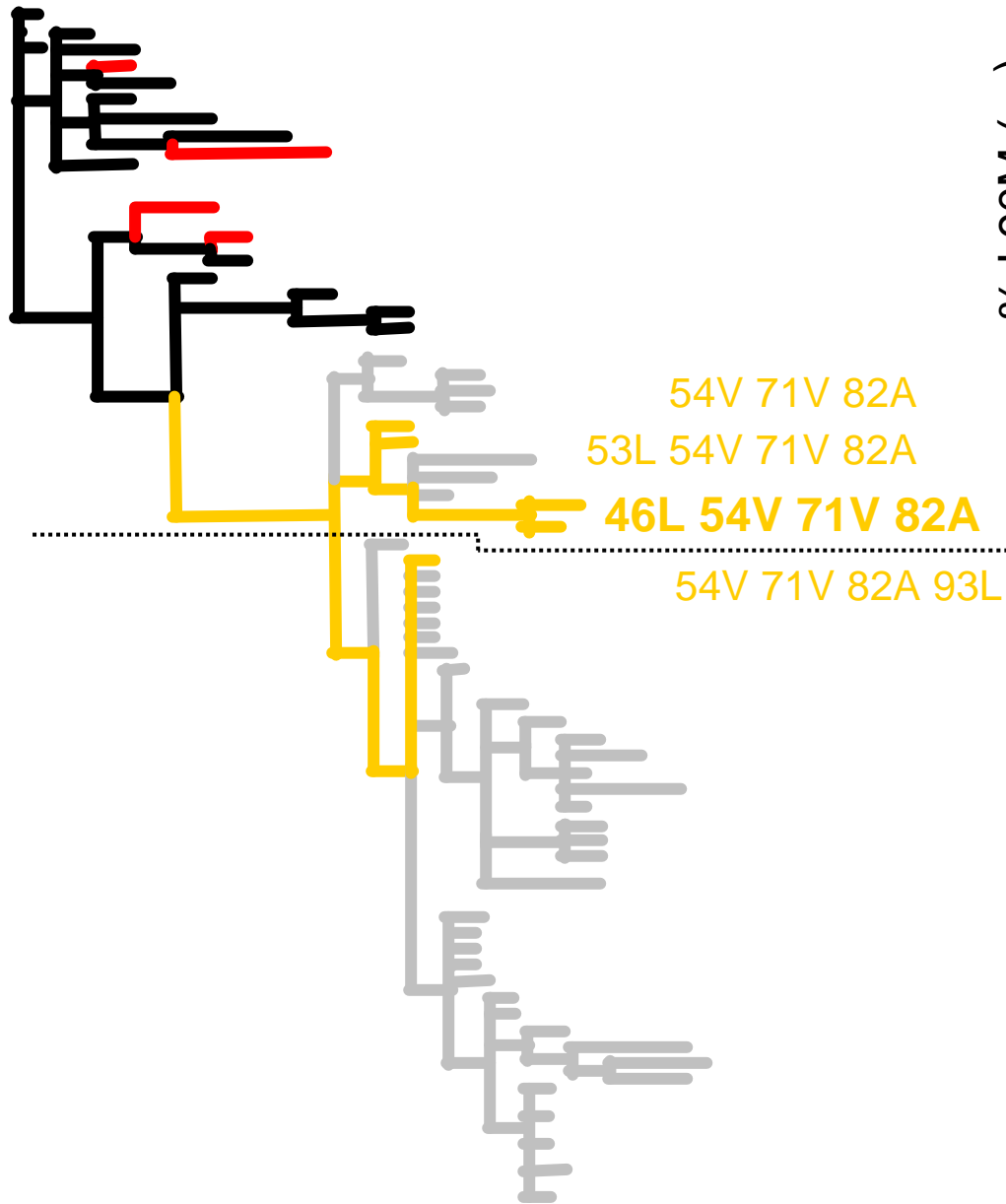


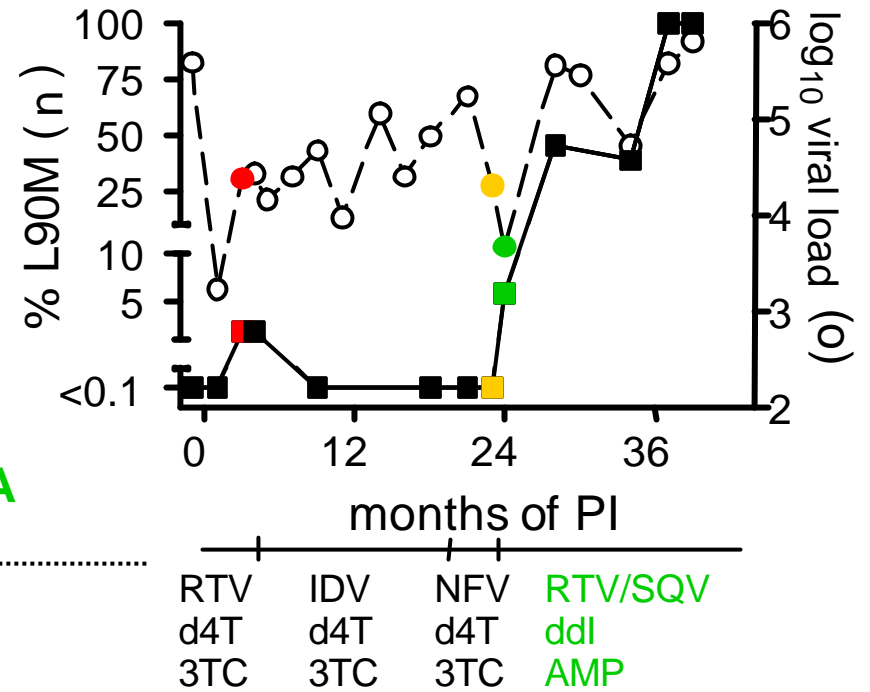
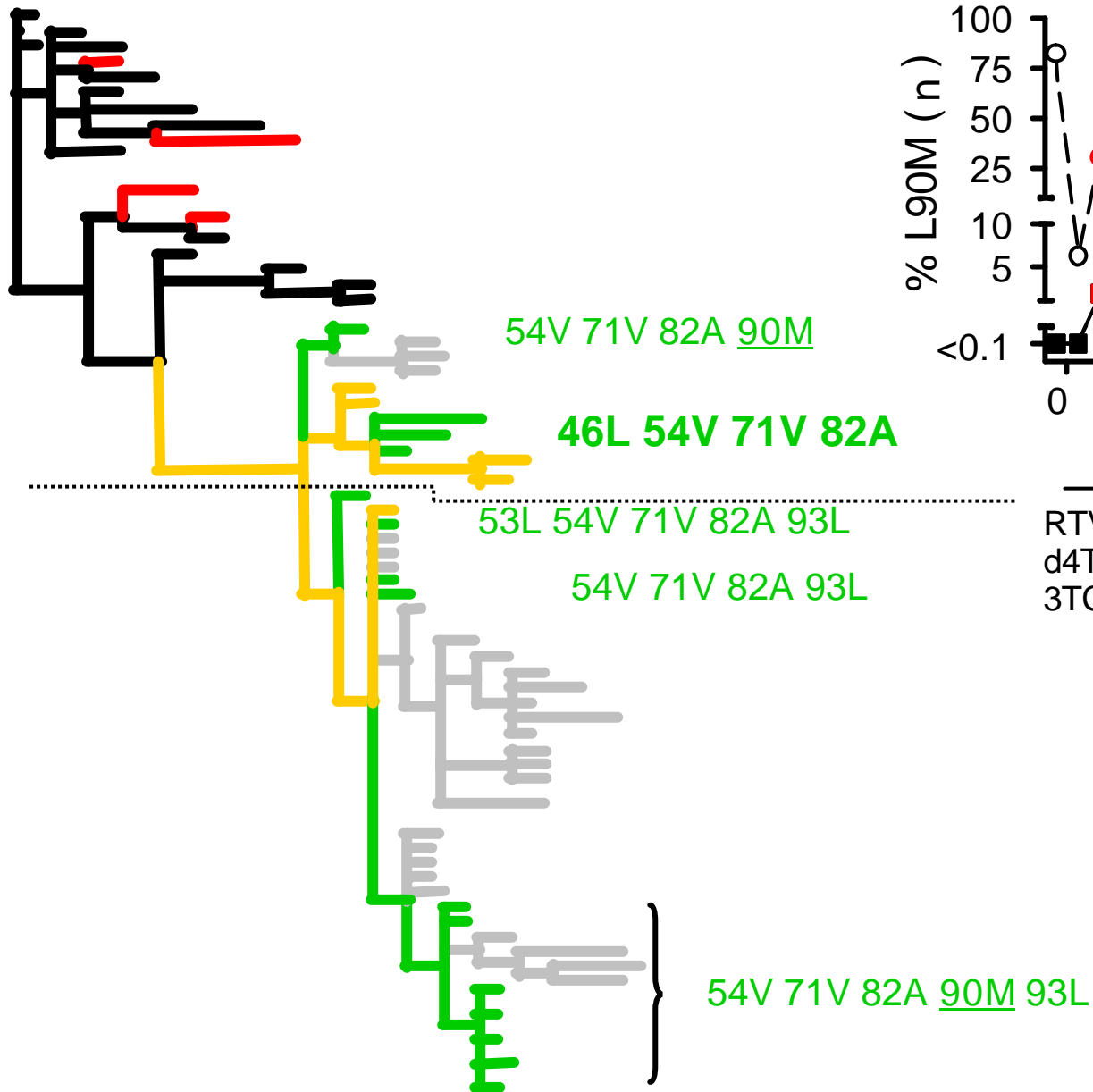
# **Resistance et diversité**

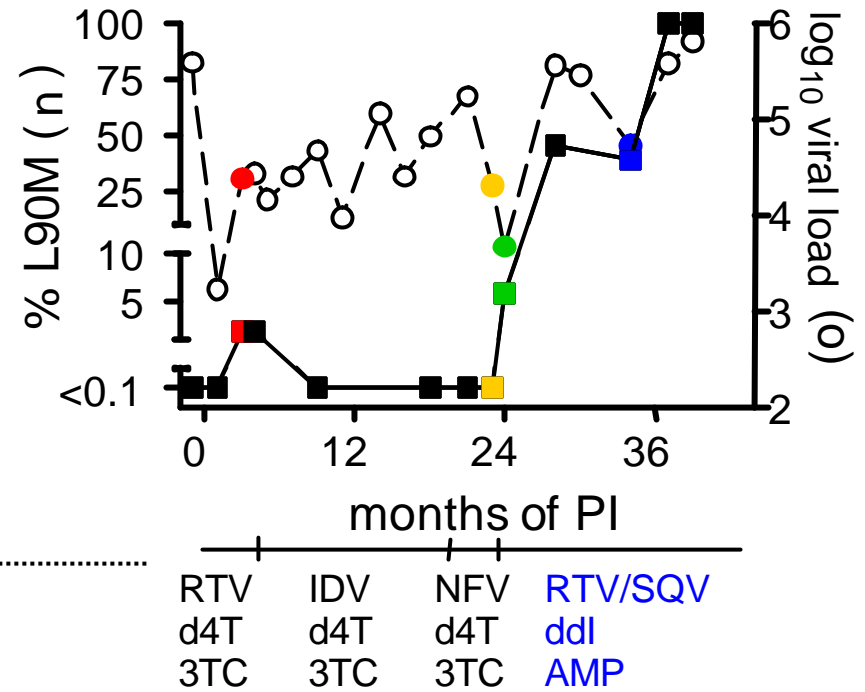
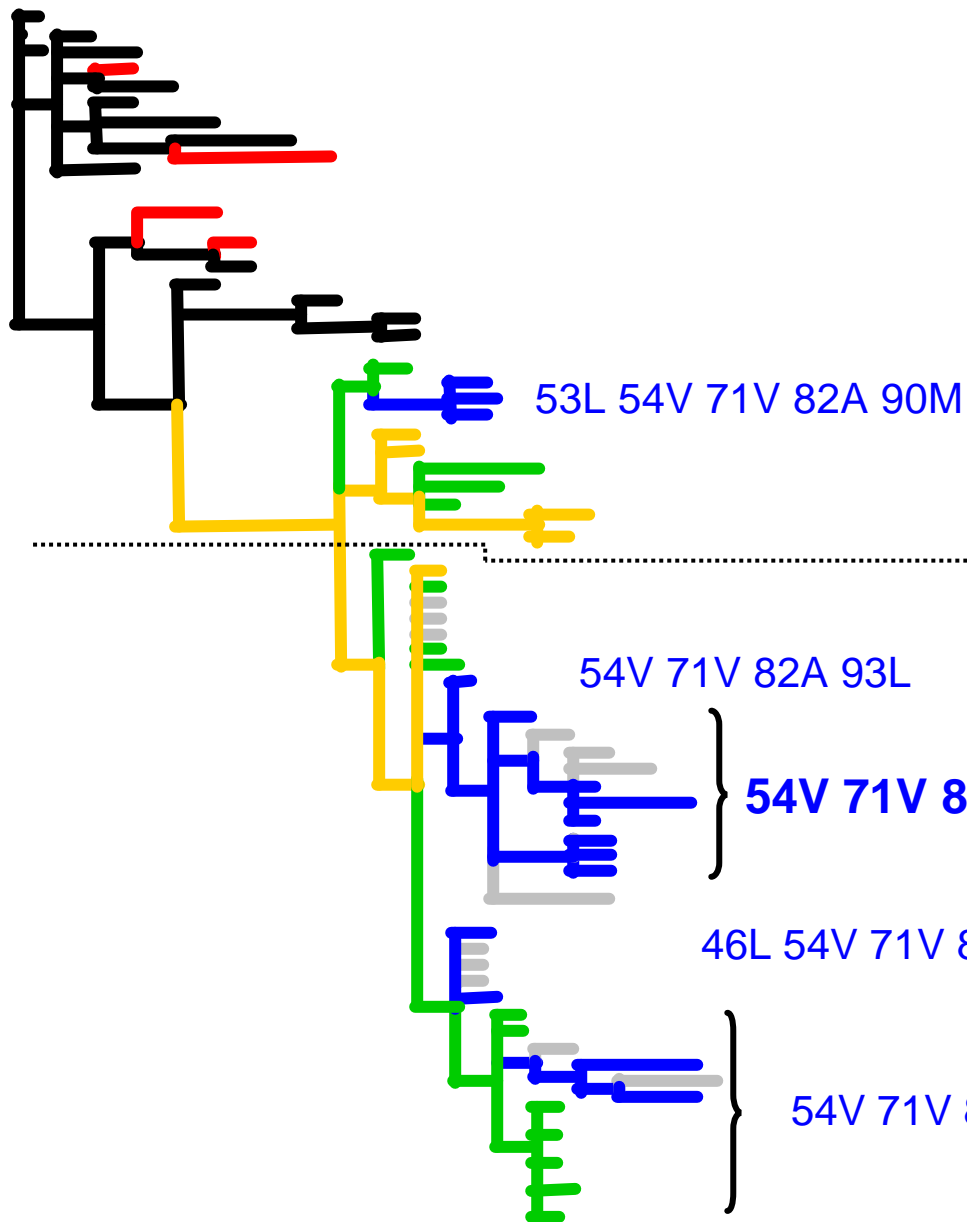
(K20R M36I L63P)

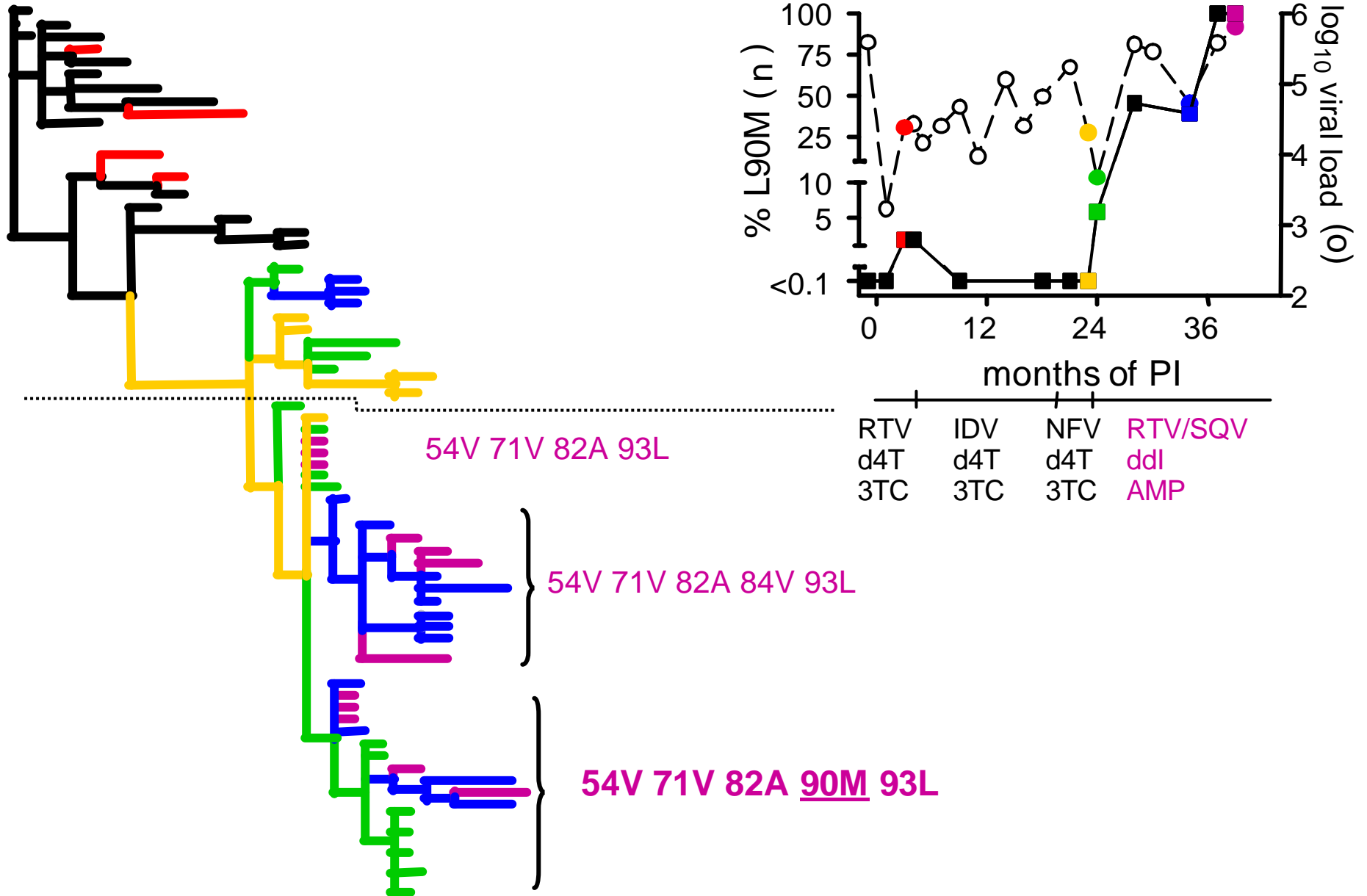












# Minority virus populations

- Minority virus populations with a variety of distinct genotypes coexist in treated patients
- Virus minorities persist throughout treatment and constantly evolve
- They can rapidly replace the prevalent majority virus, behaving as a reservoir from where new genotypes can be recruited depending on the pharmacological pressure

# Emergence of minority viruses during salvage therapy

1/132 clones

w 0    **L10I** K20V                    M36I M46I L63P A71V A73S I84V L90M

APV + LPV + RTV

w 2                    K20V                    M36I M46I L63P A71V A73S I84V L90M

w 6                    K20V **L24F** M36I M46I L63P A71V A73S I84V L90M

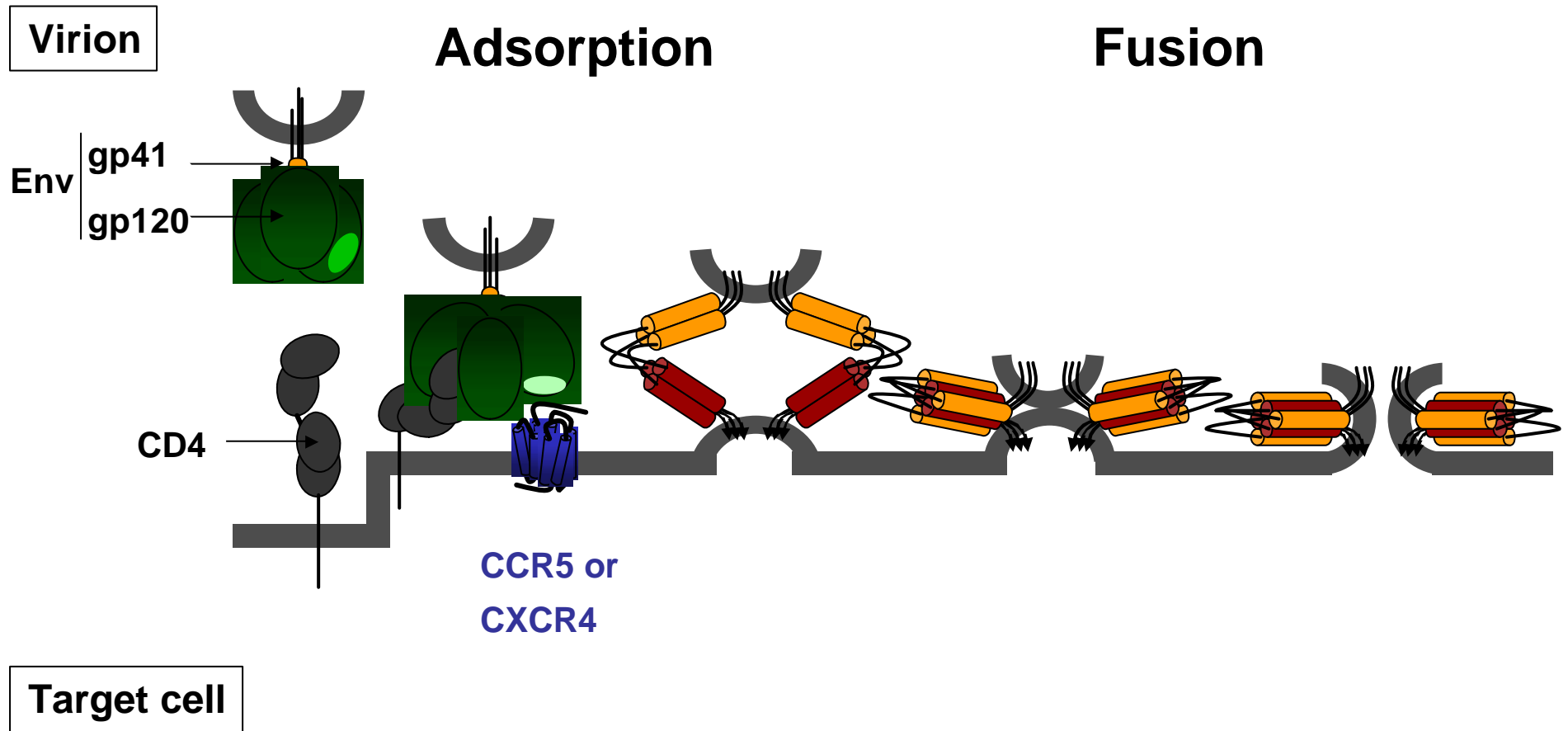
w 26    **L10I** K20V                    M36I M46I L63P A71V A73S I84V L90M

ANRS104 "Puzzle1" study : salvage by APV/LPV/RTV  
+ optimized nucleoside background

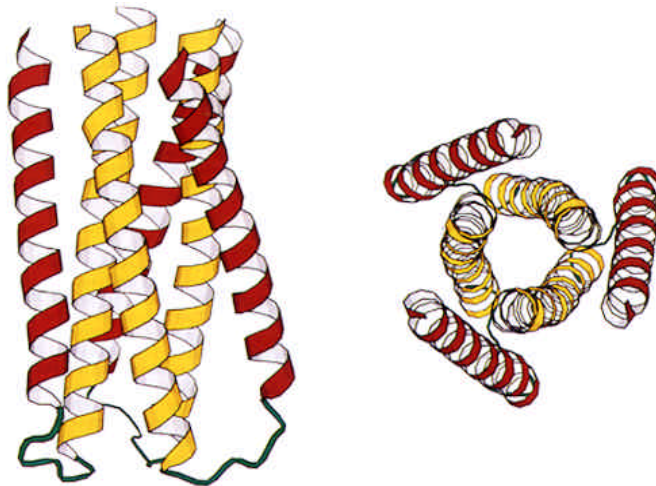
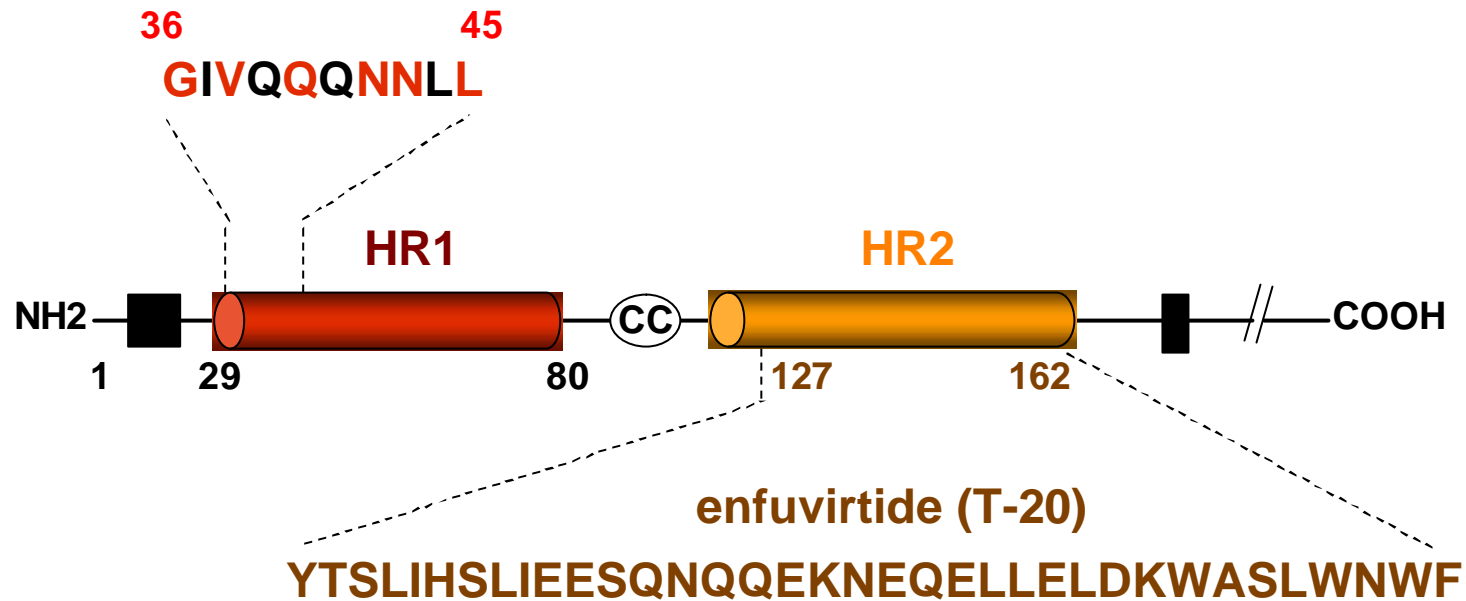
# Small genotypic changes, big resistance increases

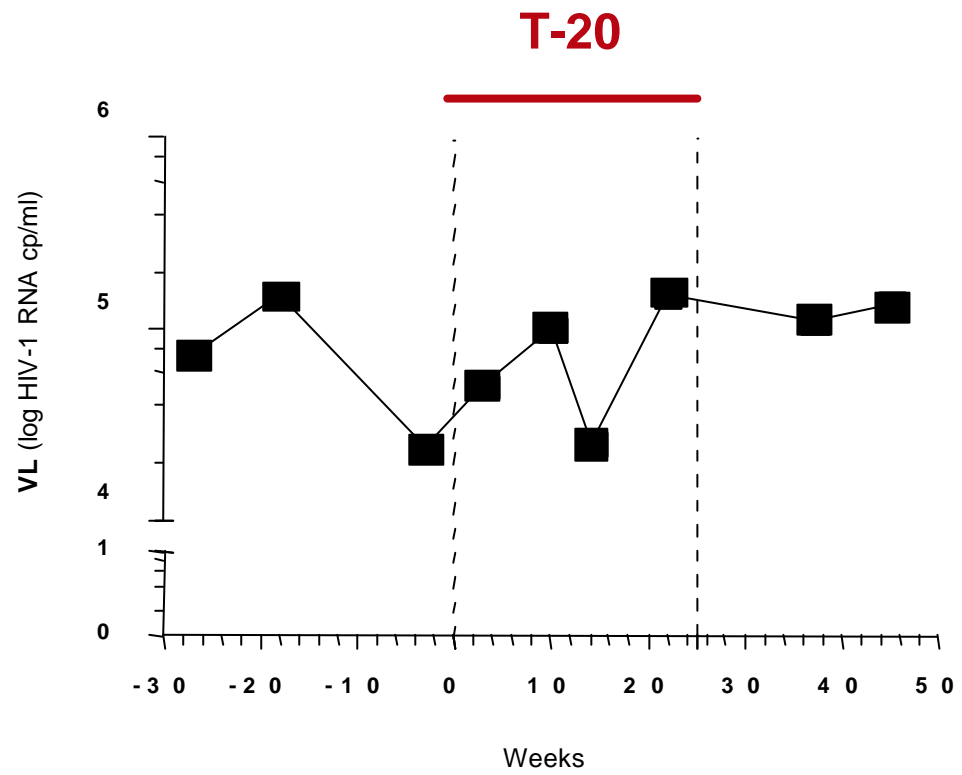
PR genotype (changes at week 26)										Week 0 APV FC	Week 26 APV FC	
L10I	L33F	M36L	M46L	I54V	L63P	A71T	I84V	L90M			3	15
L10F	K20M	M36I	M46I	I54V	L63V	A71V	G73G/S	V82A	I84V	Z	3	82
L10F	K20K/R	V32I	M36I	M46I	I47A	L63P	A71V	L90M	Z		6	52
L10L/F	K20V	M36I	M46I	L63P	A71V	G73S	I84V	L90M			11	30

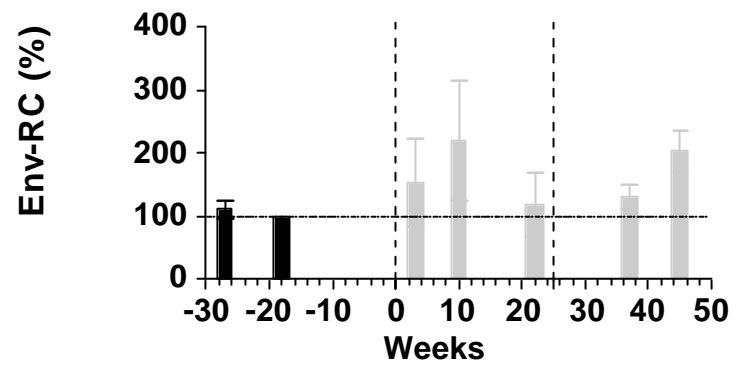
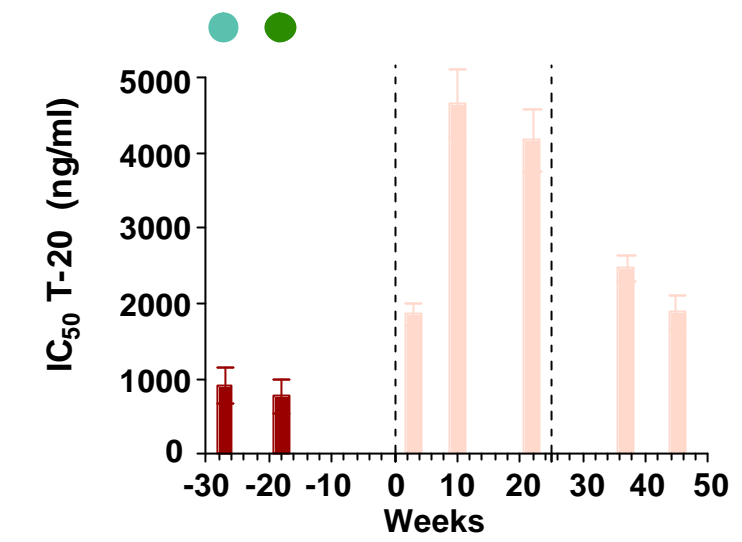
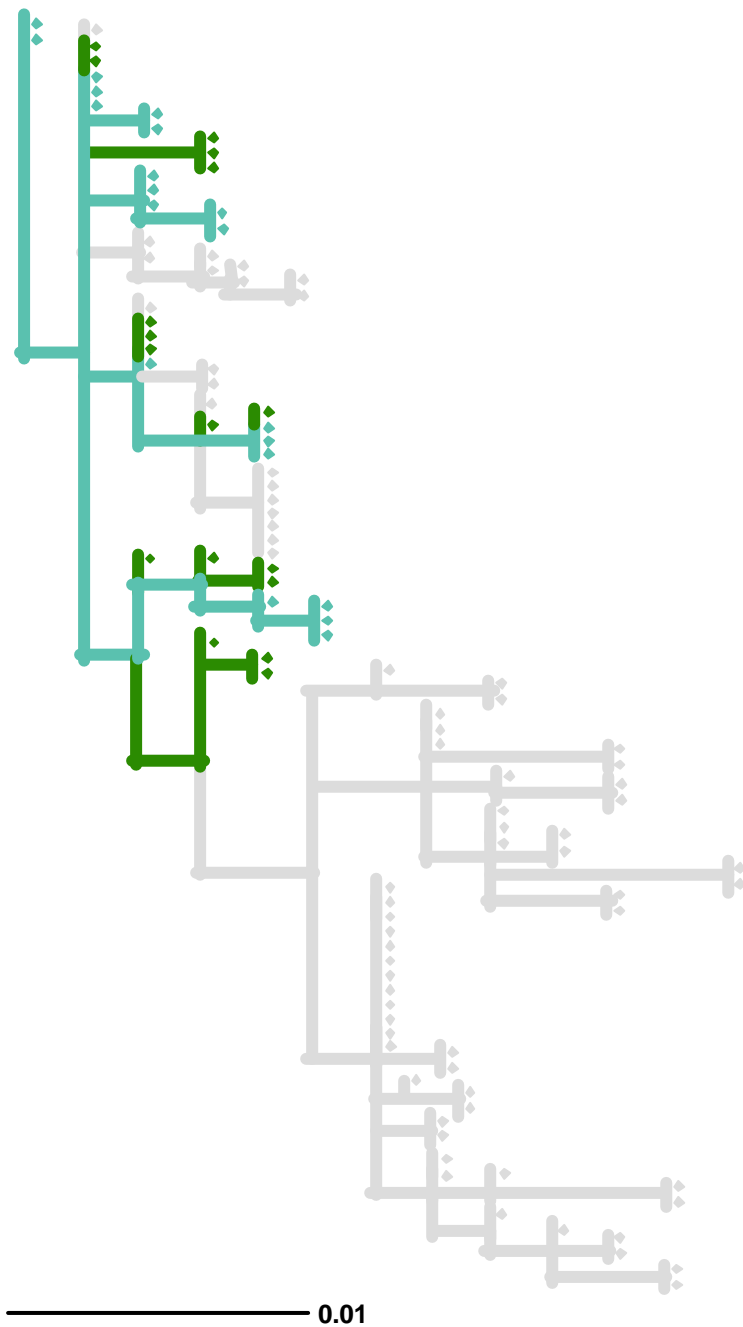
# HIV entry

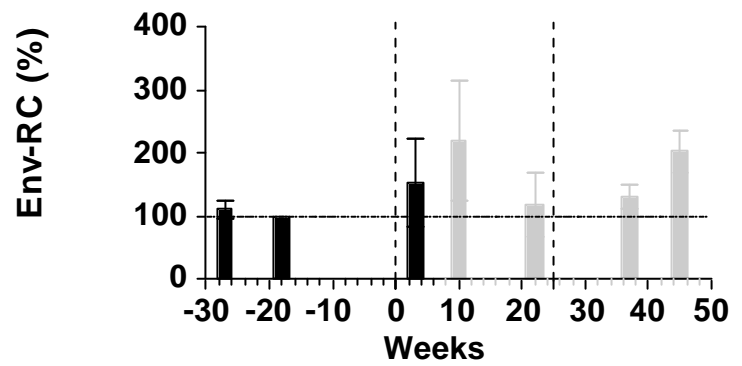
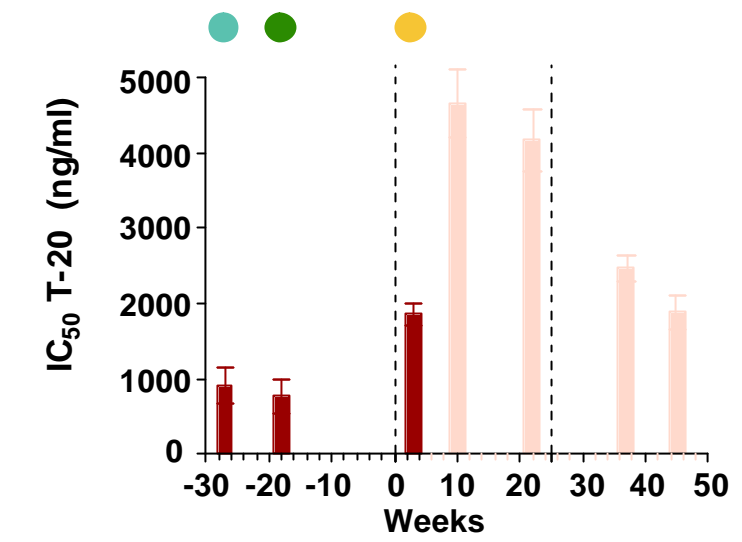
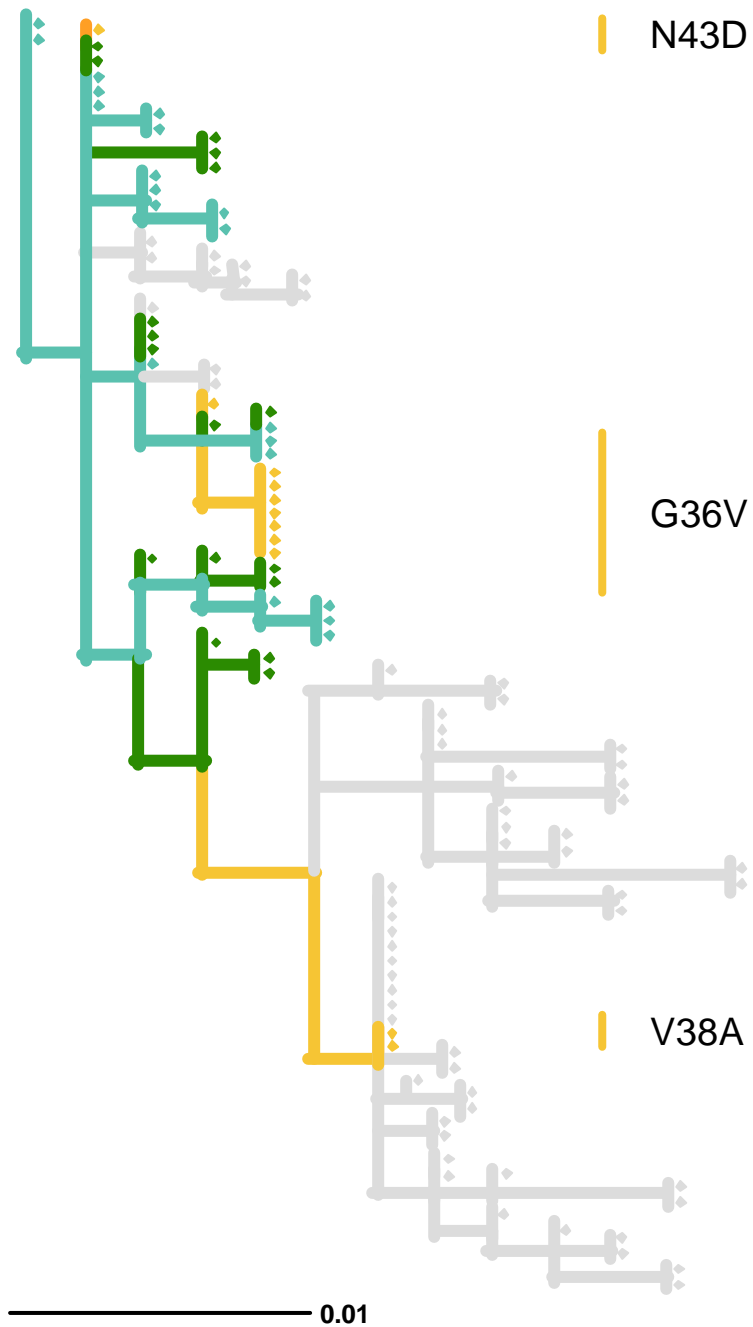


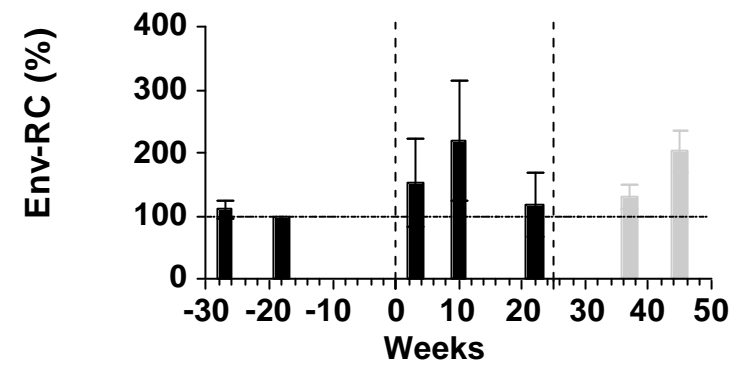
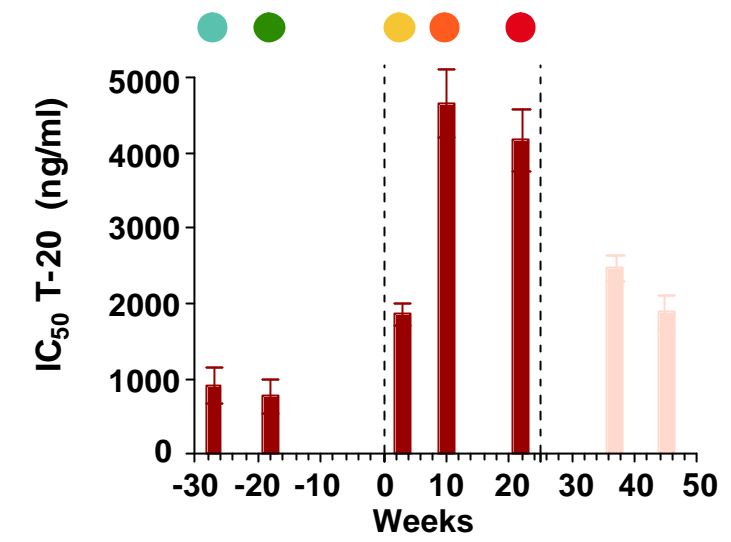
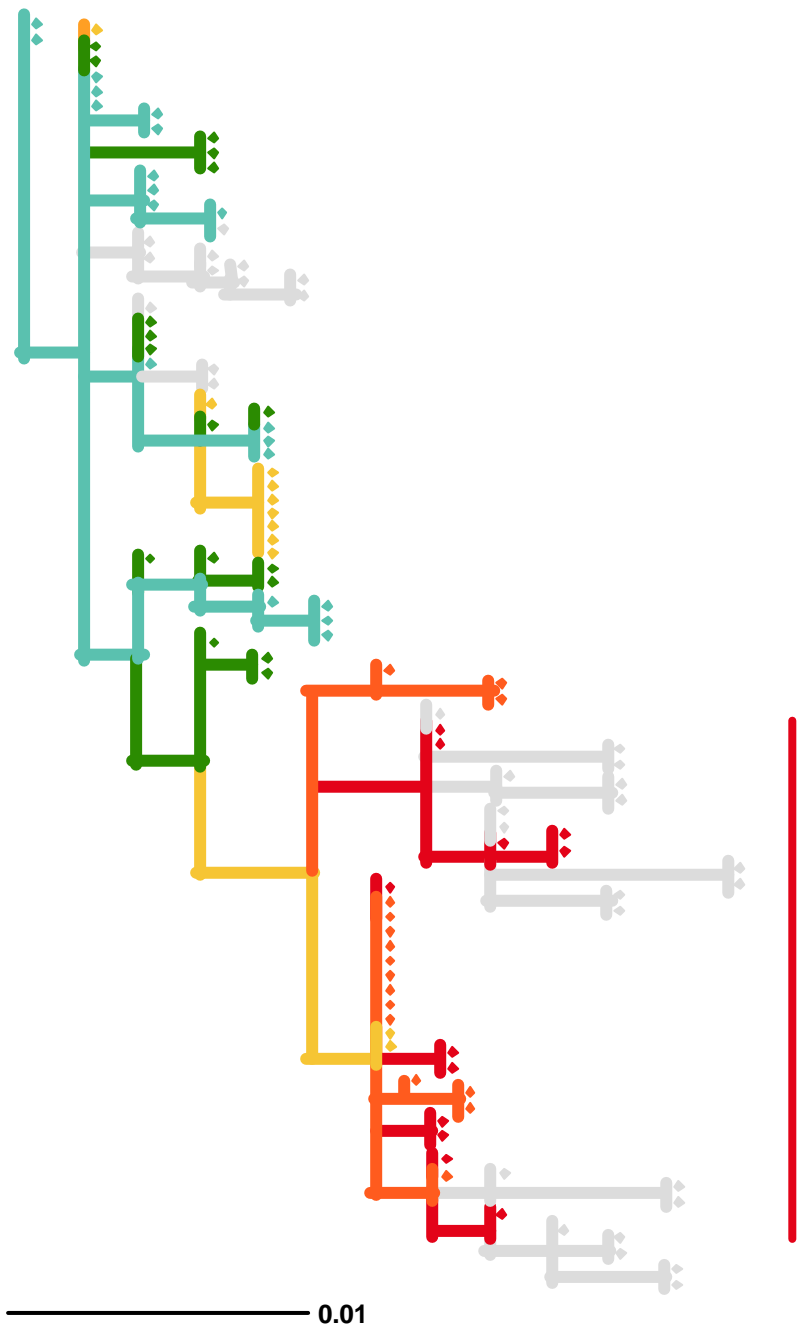
# Resistance to enfuvirtide

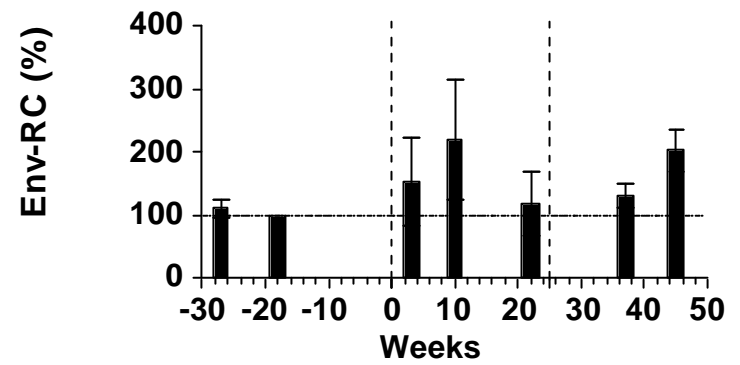
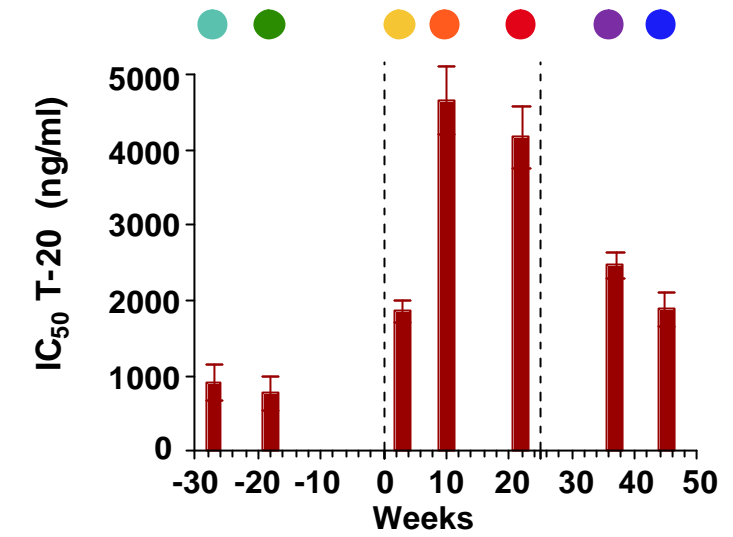
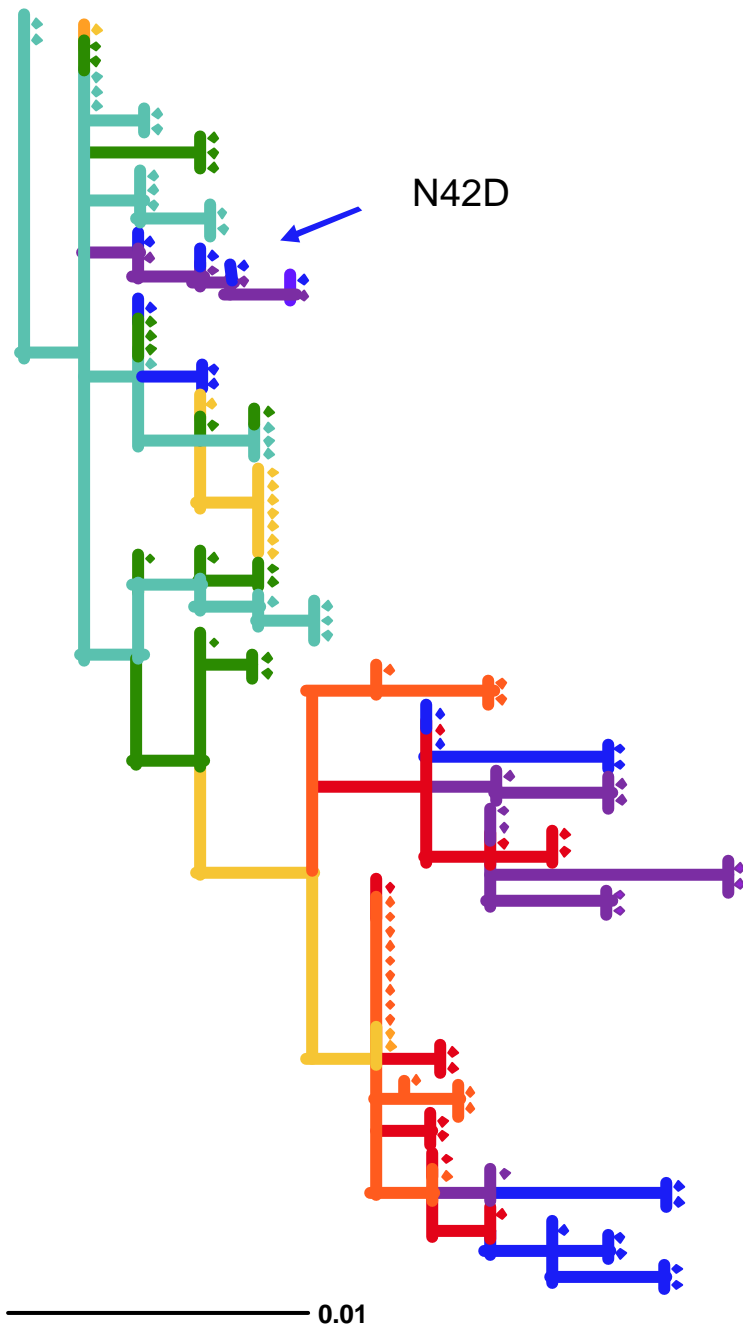












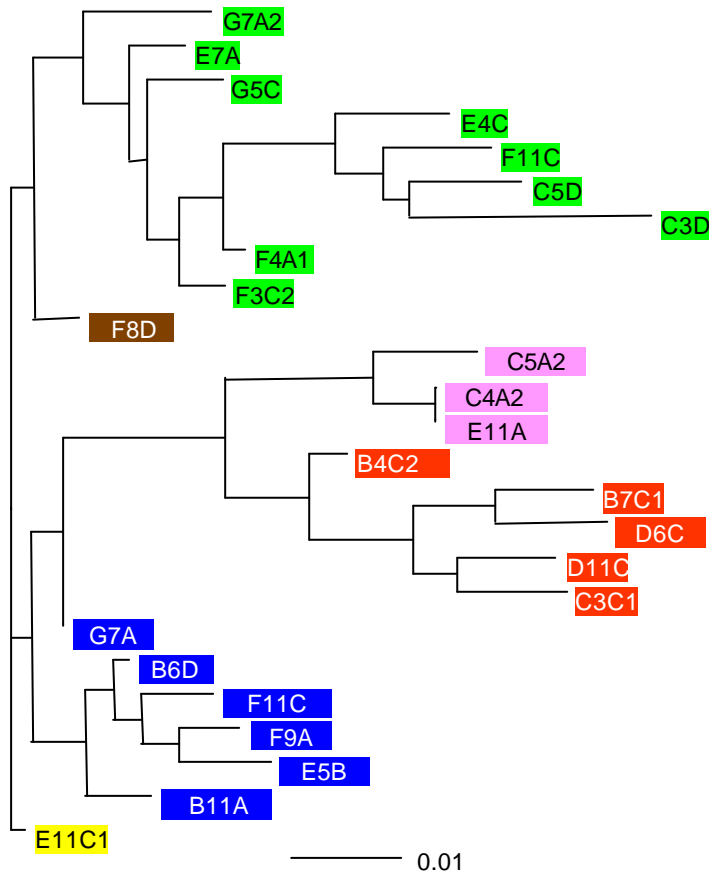
# Resistance to fusion inhibitors

- HIV resistance to fusion inhibitors is the consequence of two complementary mechanisms:
  - selection of mutations in the HR1 region of gp41
  - selection of HIV quasi-species that offer the most favorable environment for expression of these mutations
- Although not prevalent before escape, these *env* species display an apparent increase in fitness *in vitro*

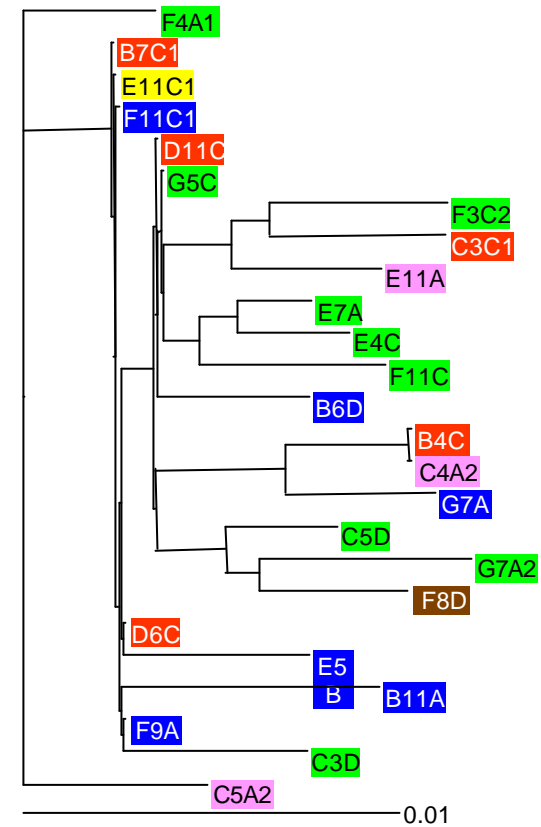
# **Preserving diversity**

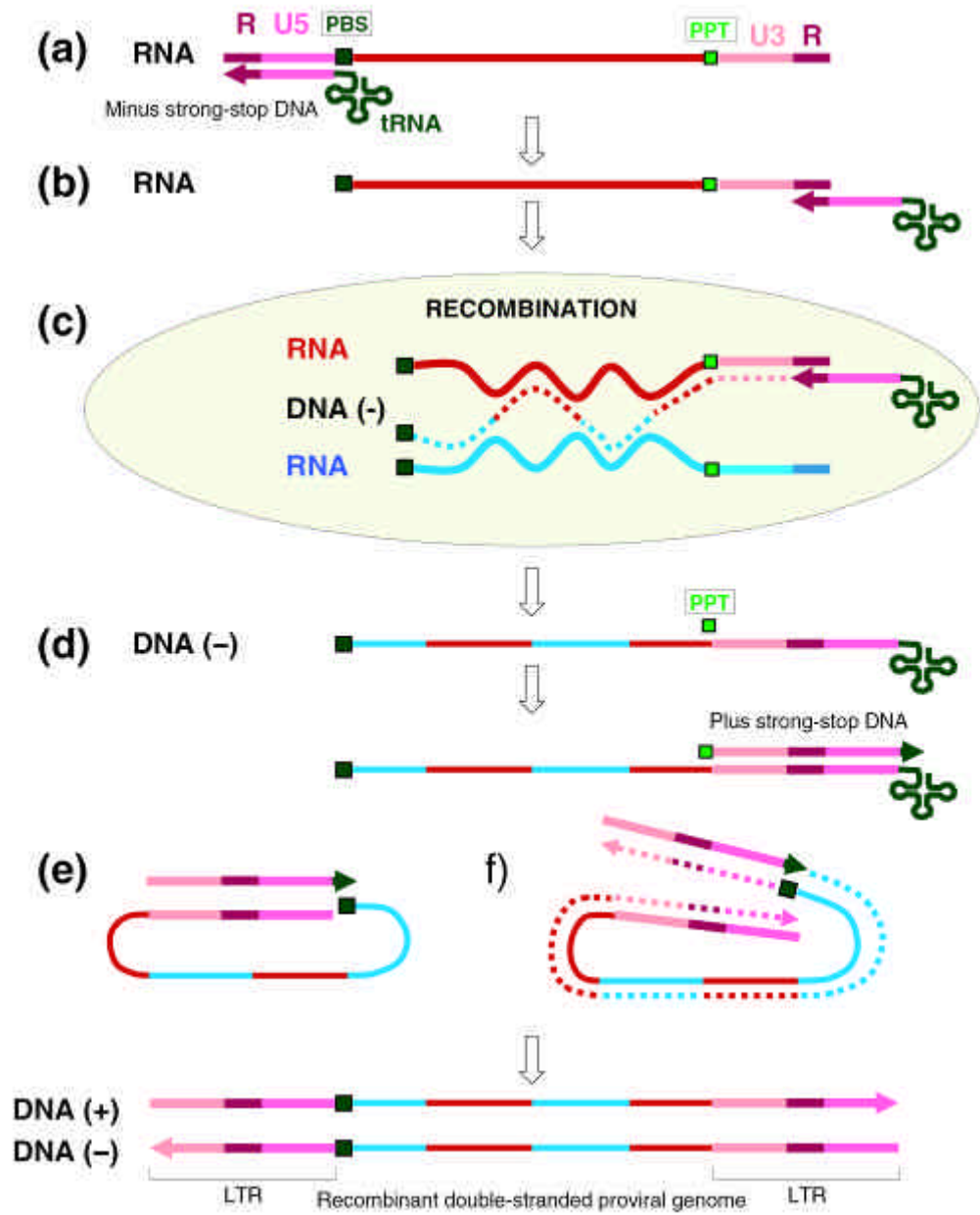
# Recombination

*Envelope C2-V4*

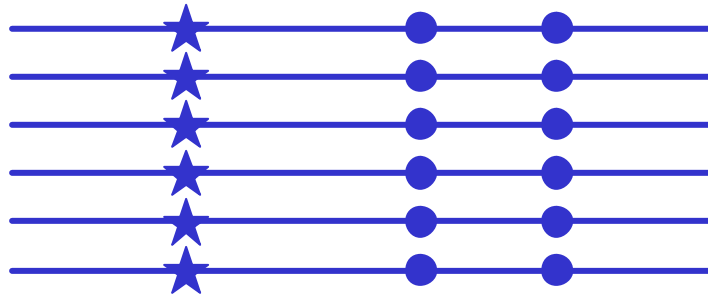
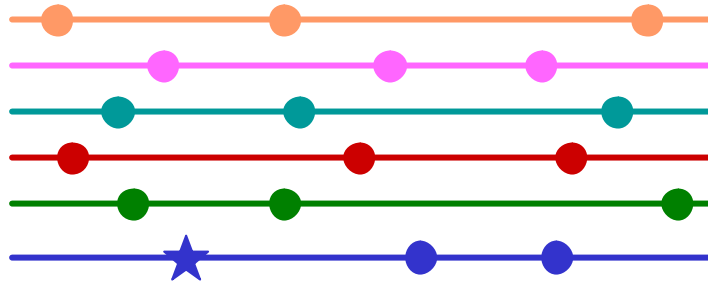


*Protease + RT*



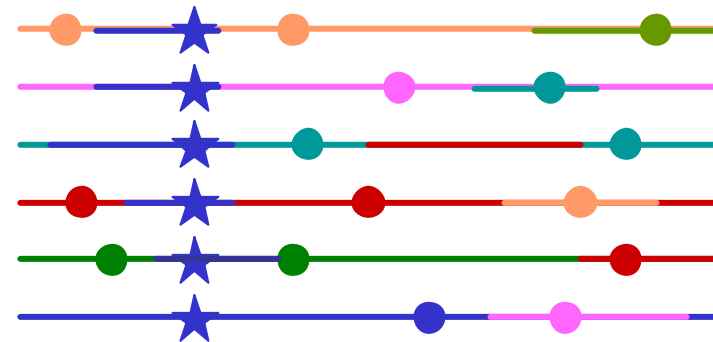
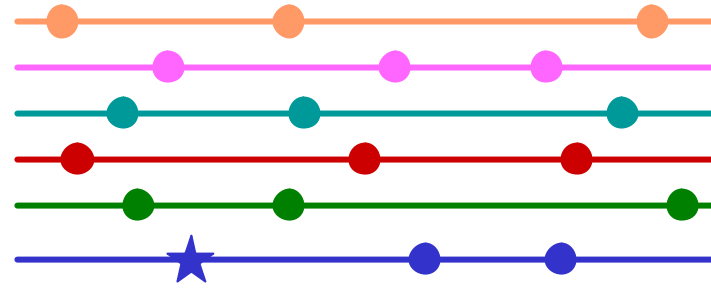


## no recombination



Loss of viral diversity

## recombination



Preservation of diversity