



# **The *In Vitro* Resistance Profile of NcRTI-1 is Complementary with the Resistance Profile of Tenofovir and Zidovudine**

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# **The Resistance Profile of NcRTIs**

## **Complementarity with Tenofovir and Zidovudine**

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# A Novel Mechanism of RT Inhibition



- **Potent Inhibitor of HIV Replication**  
( $EC_{50} = 30 \text{ nM}$ ,  $SI > 300$ )
- **Active on NNRTI-resistant HIV strains and HIV-2**
- **Blocking the Active Site of HIV RT ( $IC_{50} = 320 \text{ nM}$ )**
  - Nucleotide-competitive RT Inhibitor
  - Formation of Dead-end complex (NcRTI-RT-Primer/Template)



NcRTI-1

# A Novel Mechanism of RT Inhibition

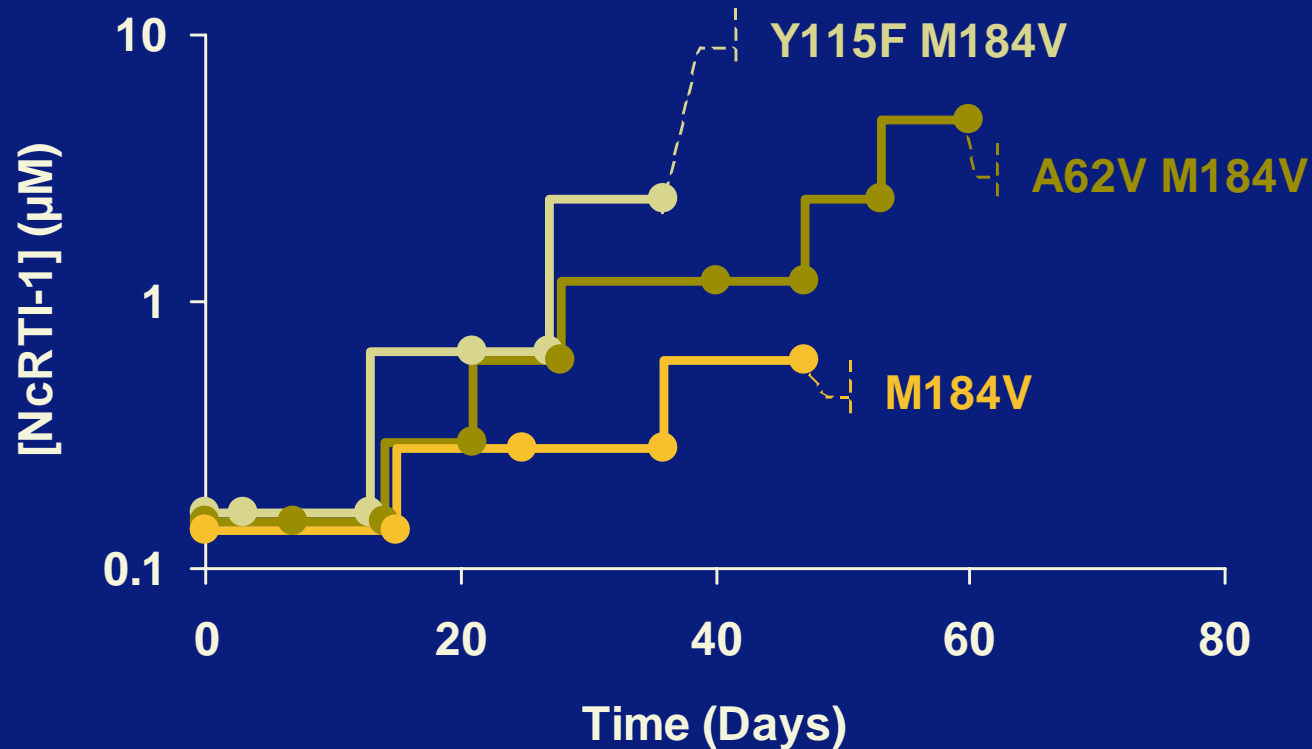


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- **Novel Mechanism → Novel Resistance Profile**



NcRTI-1

# *In vitro* Resistance Selection with NcRTI-1



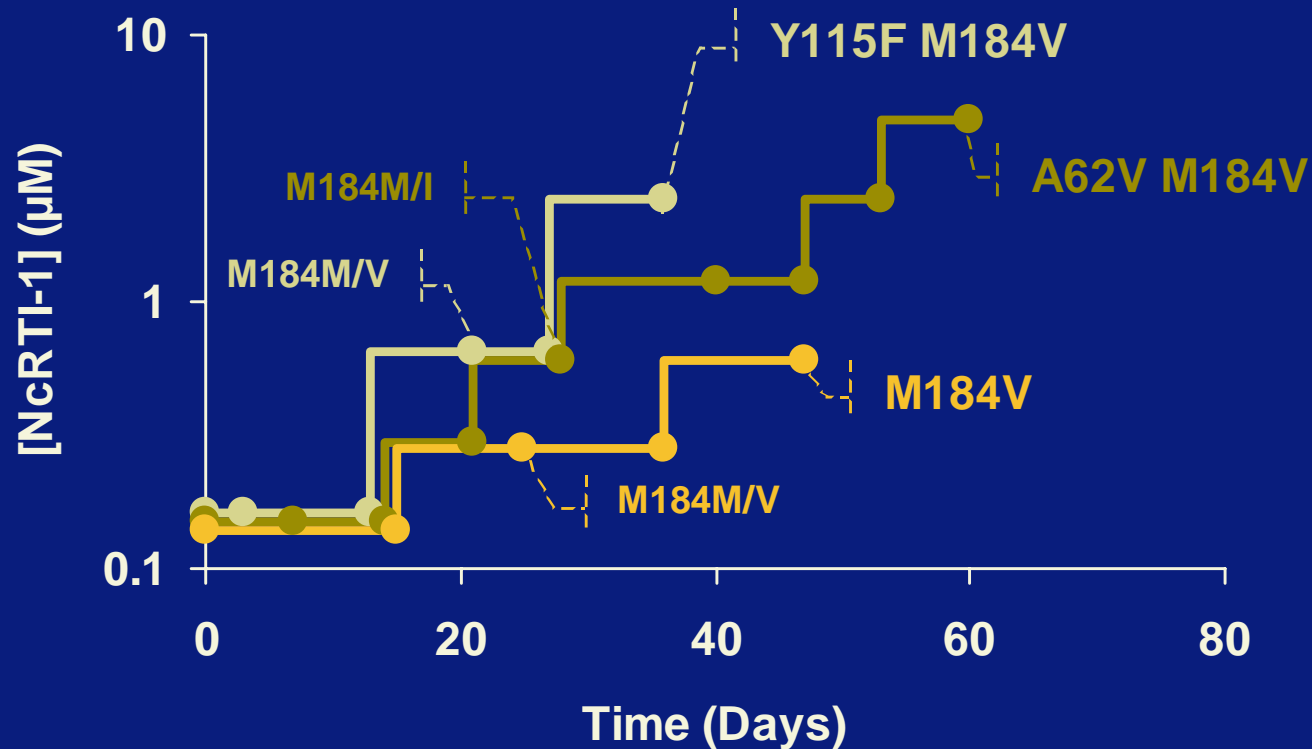
Start strain:

- HIV wildtype IIB

- Clinical Isolate A (M41L E44D D67N K103N V118I L210W T215Y K219K/Q ...)

- Clinical Isolate B (M41L E44D D67G S68G L74V K103N V106I V118I L210W T215Y K219D M230L ...)

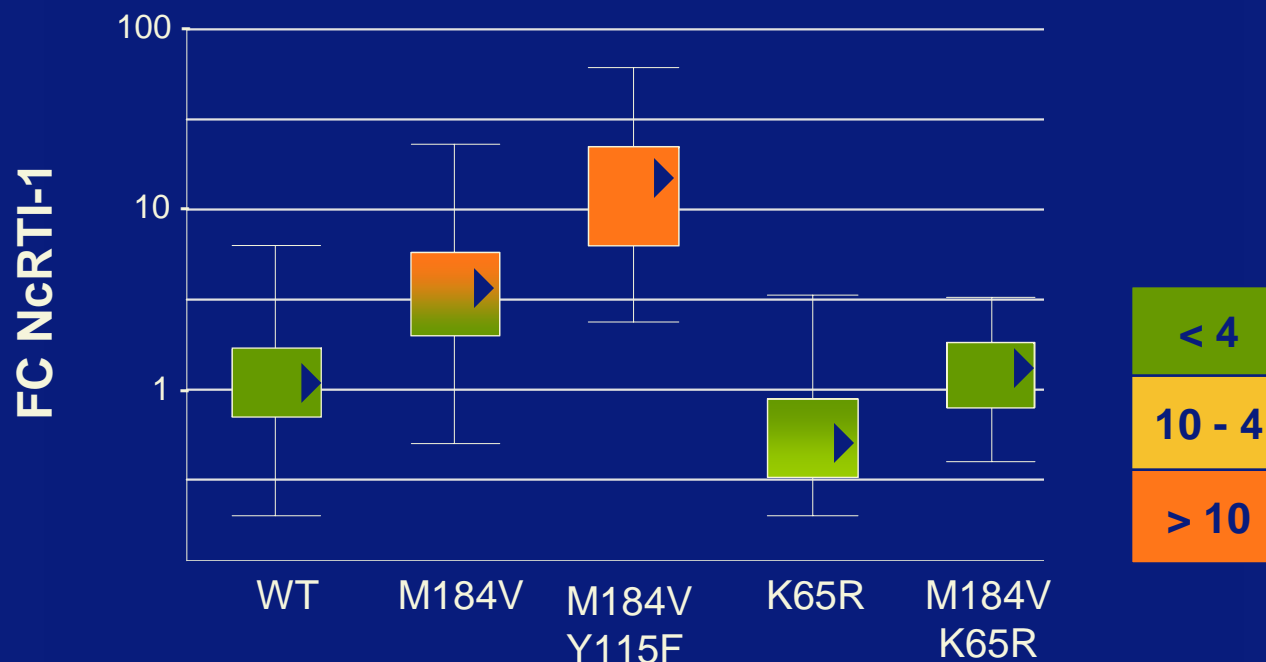
# *In vitro* Resistance Selection with NcRTI-1 tibotec



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# Susceptibility to NcRTI-1 of 1700 Clinical HIV-1 Isolates



- M184V, Y115F and K65R are associated with a change in NcRTI-1 susceptibility

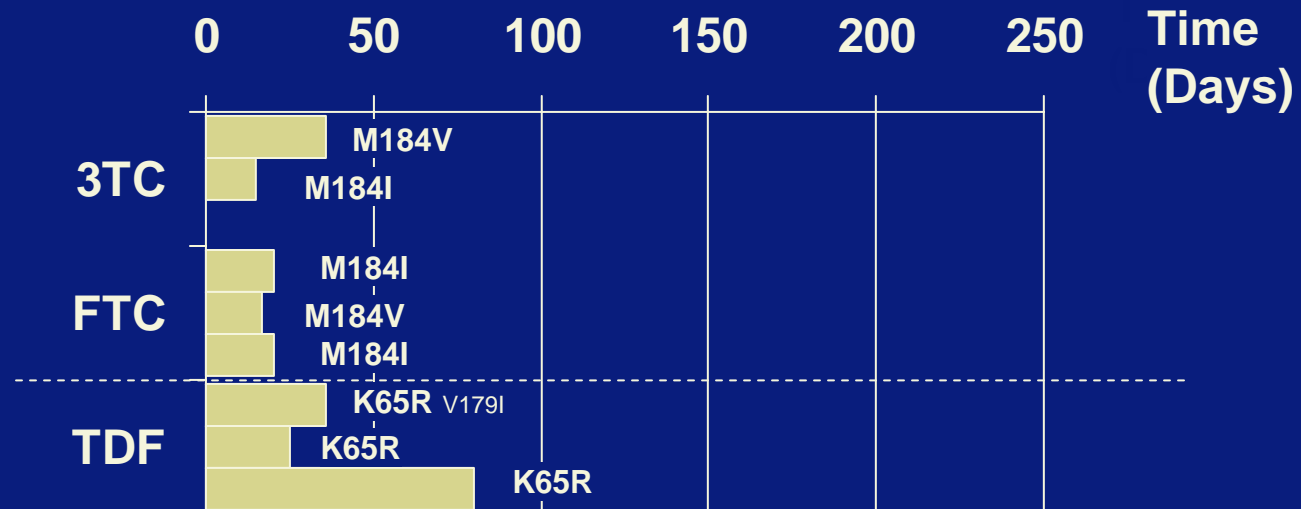
# NcRTI Resistance Pattern



- Susceptibility of site-directed mutant HIV-1 strains

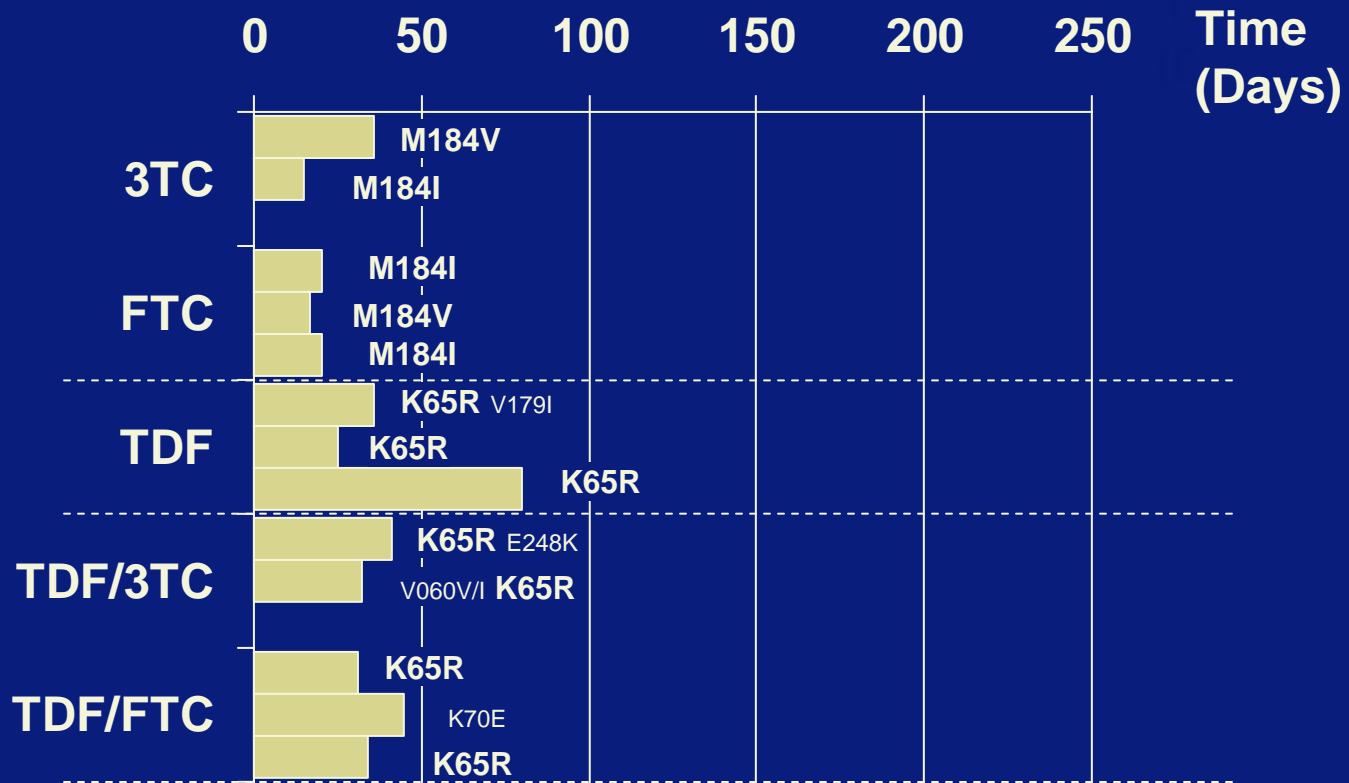
FC of EC <sub>50</sub>	NcRTI-1	3TC	ZDV	TDF	
M184V	5.0	> 100	1.0	0.8	
Y115F	7.9	0.7	0.9	1.0	
Y115F M184V	75	> 100	0.5	0.9	
K65R	0.5	> 20	2.0	6.0	
K65R M184V	0.9	> 100	1.1	2.3	
M41L D67N K70R T215Y	3.0	8.1	67	3.3	< 4
T69S ins69-70S-S L210W T215Y	0.9	9.5	53	2.3	10 - 4
A62V V75I F77L F116Y Q151M	1.0	5.4	> 100	3.7	> 10

# NcRTIs Prevent the Selection of K65R



Experiment stopped when M184V or K65R appeared

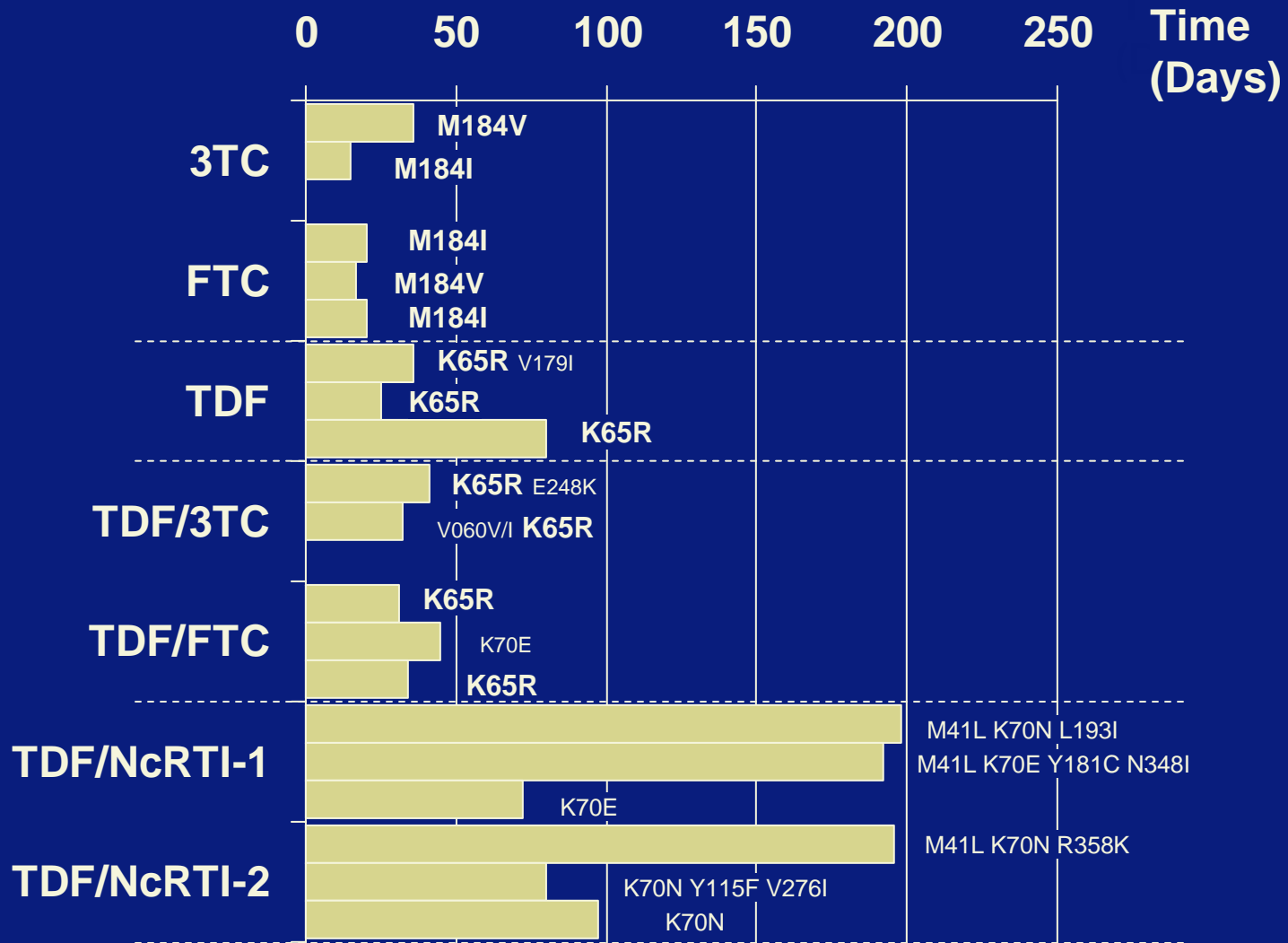
# NcRTIs Prevent the Selection of K65R



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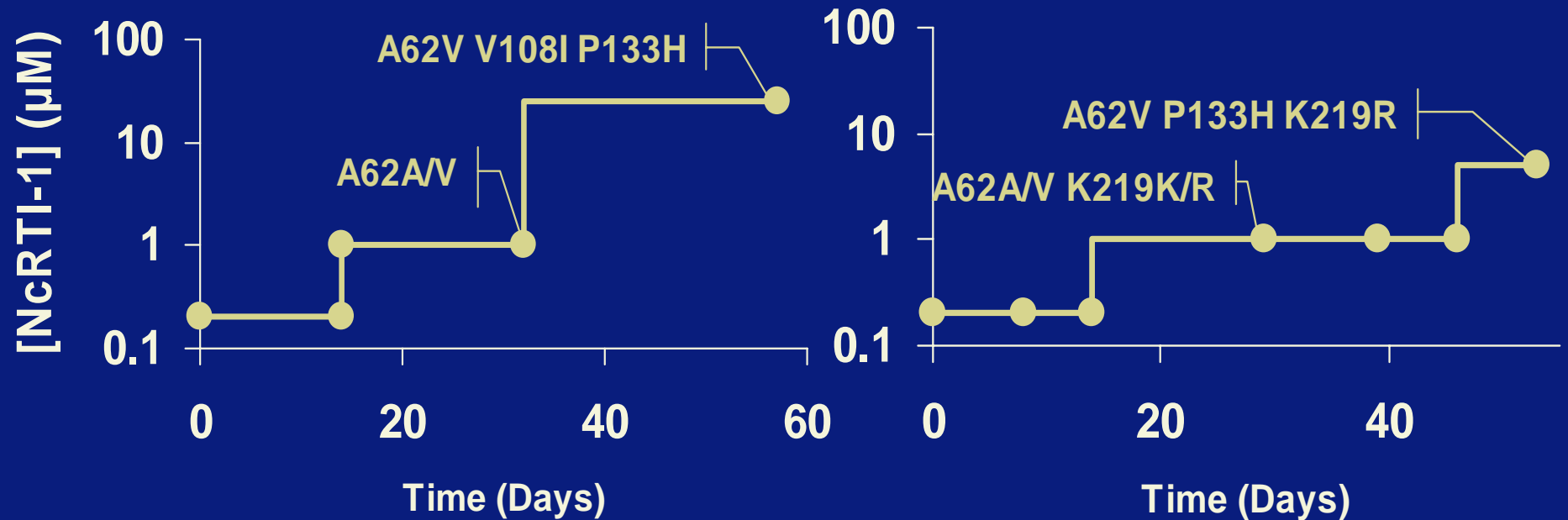
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# *In vitro* Resistance Selection with NcRTI-1



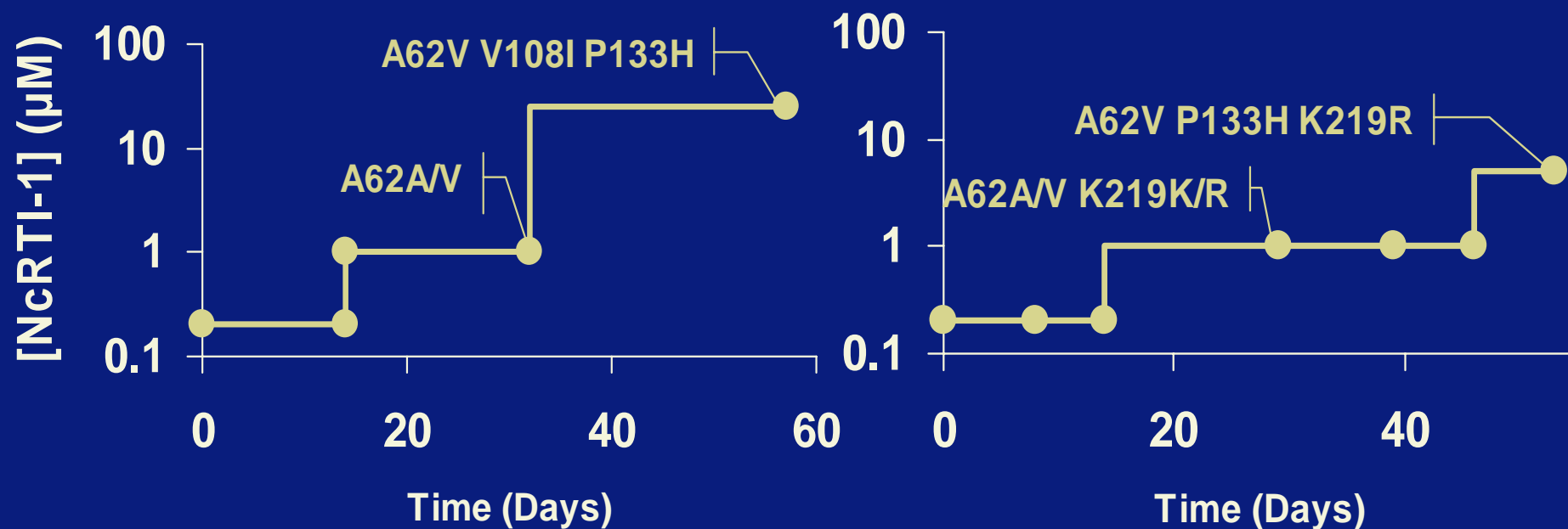
Starting from ZDV resistant strain (M41L D67N K70R T215Y)



# In vitro Resistance Selection with NcRTI-1



Starting from ZDV resistant strain (M41L D67N K70R T215Y)



	FC EC <sub>50</sub>	NcRTI-1	ZDV	
M41L D67N K70R T215Y		3.0	63	
M41L <b>A62V</b> D67N K70R T215Y		2.7	3.6	
M41L D67N K70R <b>P133H</b> T215Y		2.3	0.6	< 4
M41L <b>A62V</b> D67N K70R <b>P133H</b> T215Y		26	2.0	10 - 4
<b>A62V P133H</b>		9.1	0.8	> 10

# NcRTI Resistance Profile



The pathway to NcRTI resistance starts with the selection of M184V

- the loss of susceptibility associated with M184V is limited
- additional mutations are necessary for > 10 fold resistance to NcRTIs
- K65R is associated with hypersusceptibility to NcRTIs

In a TAM background (M41L D67N K70R T215Y) the selection of A62V & P133H reverses zidovudine resistance.

The NcRTI resistance profile is complementary to the resistance profile of tenofovir and zidovudine.

# Acknowledgements



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**The End**

