Subtype Differences in Regard to Development of HIV Drug Resistance to Dolutegravir and Other Compounds

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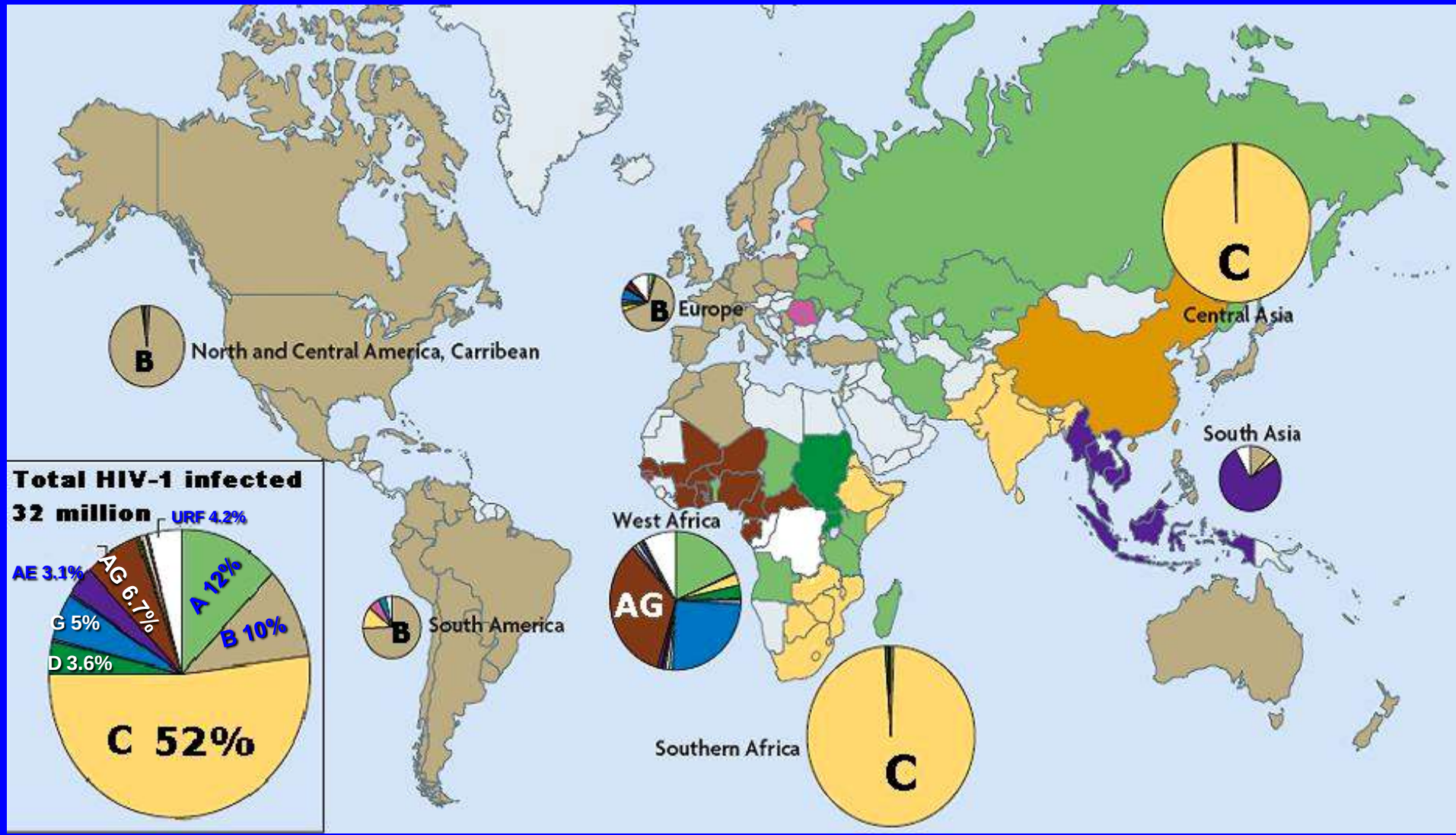
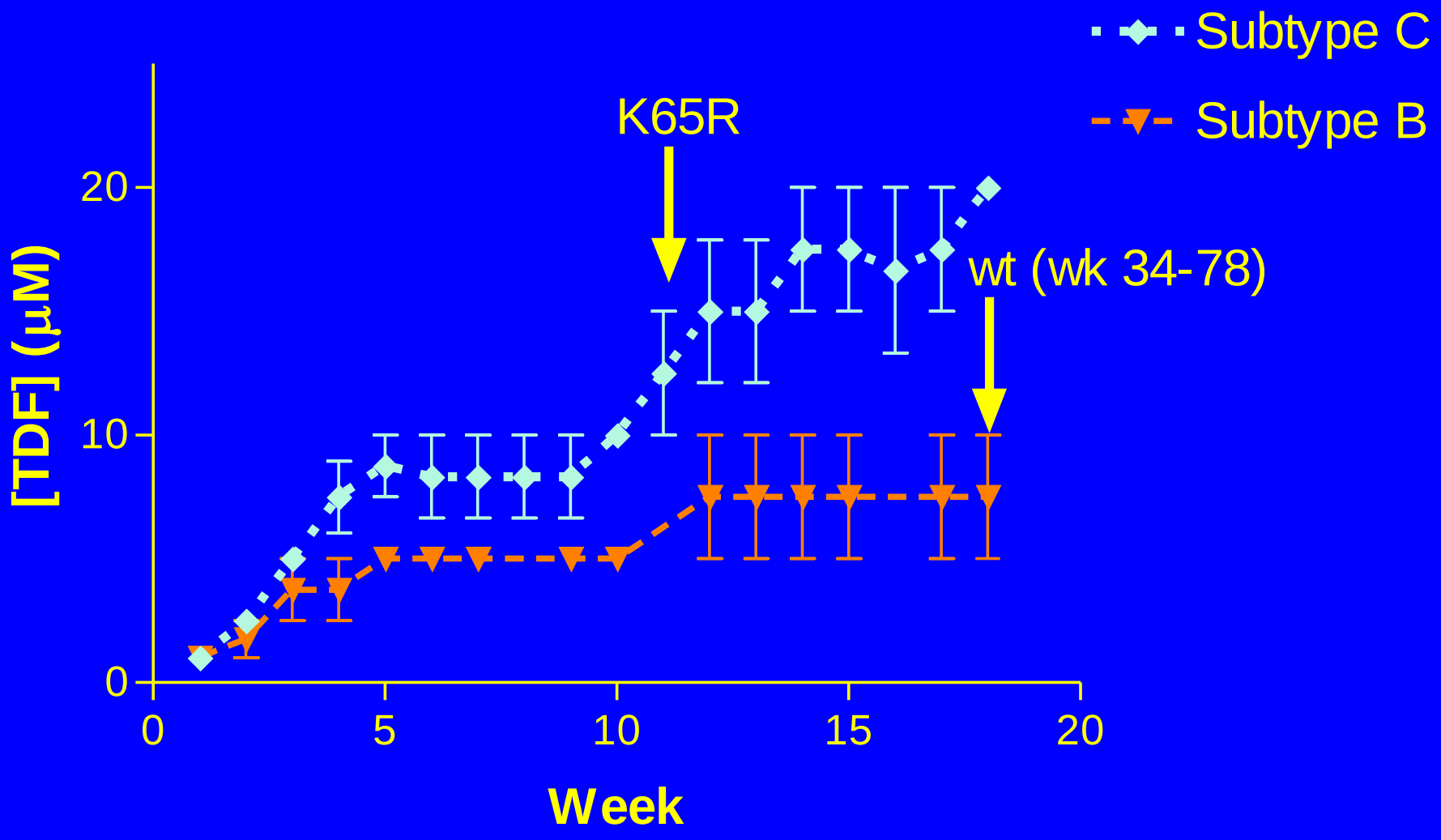
Global distribution of HIV-1 subtypes



Silent Mutation at Codon 106 responsible for the V106M mutation in clade C RT with NNRTIs

HIV-1 RT	Clade B	Clade C
Wild type codon at position 106	V(GTA)	V(GTG)
In clade C, V106M arises	two codon changes	M(ATG)
In clade B, V106A occurs	A(GCA)	two codon changes

Rapid Selection of K65R Resistance in Subtype C Isolates



History of 23 Botswana Patients Treated with ddI/d4T plus 3TC or NVP

No. Patients	23
No. Patients failing	15
No. Patients with K65R	7
No. Patients with L74V	0

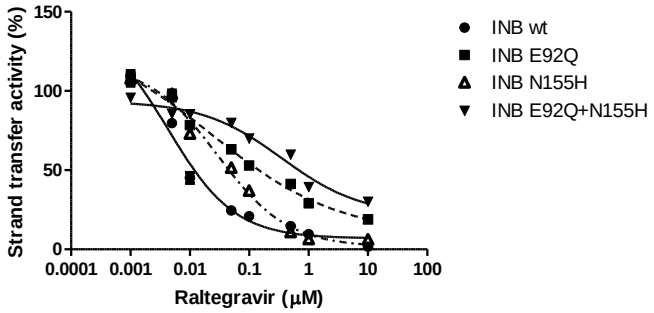
Mutations in MT-2 Cells after 10 Weeks

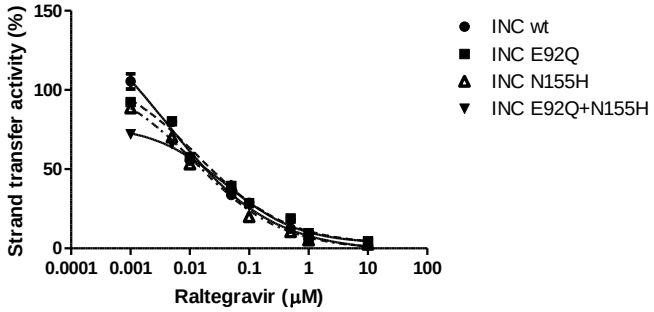
DRUG	VIRUS			
	NL4-3 (wt)	NL4-3 (64)	NL4-3 (65)	NL4-3 (64/65)
3TC	M184I	Not done	Not done	M184I
FTC	M184I	M184I	M184I	M184I
ABC	M184I	M184I	M184I	**K65R**
ddI	L74V	M184I	V75I	**K65R**
d4T	None	None	None	**K65R**
TNF	None	None	None	**K65R**

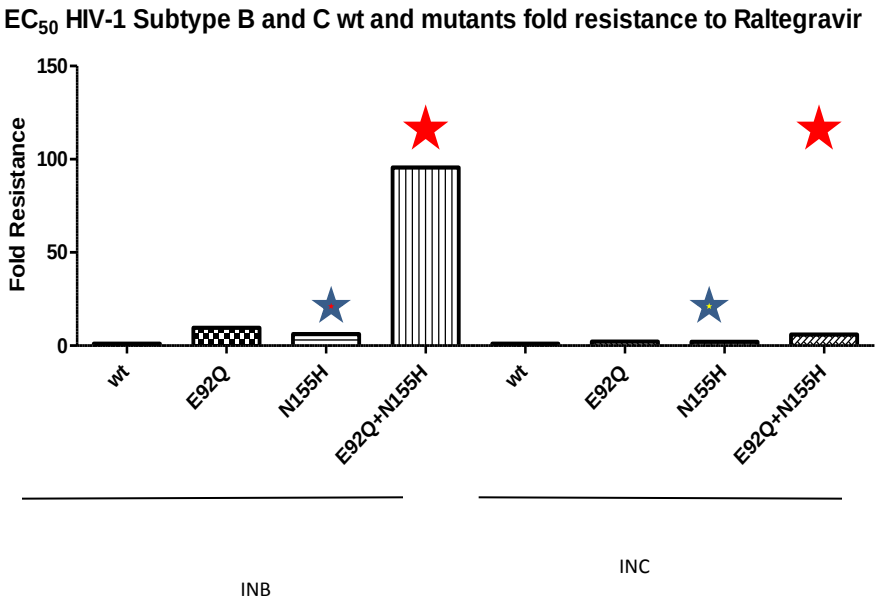
Alignment of subtype B and C integrases

Alignment of subtype B integrase cloned from the subtype B HIV-1 molecular clone pNL4-3 and subtype C integrase cloned from the subtype C HIV-1 molecular clone pINDIE-C.

Fold-resistance to Raltegravir - comparisons of subtypes







Conclusions

- Polymorphic differences within the subtype B and C integrase genes likely cause variations in the contribution of N155H alone or in combination with E92Q to drug resistance.
- It is possible that different viral subtypes may favour different mutational pathways, potentially leading to varying levels of drug resistance among different subtypes.

HIV-1 integrase gene mutation R263K confers resistance to the integrase strand transfer inhibitor Dolutegravir

Resistance to Integrase strand transfer inhibitors

INSTI	Major resistance mutations	Minor resistance mutations
RAL	E92Q, Y143R/C/H, Q148R/K/H, N155H	Multiple
EVG	E92Q, T66I, Q148R/H/K, N155H	Multiple
DTG	-	T124A, S153F/Y, L101I

NEW INSTI: DOLUTEGRAVIR (DTG)

Selection results with DTG

Subtype	Virus	Baseline polymorphisms	Week 20		Week 37	
			DTG Concentration (mM)	Acquired mutations	DTG Concentration (mM)	Acquired mutations
B	5331	I72V	0.05	R263K		
	BK-132	M154I, V201I	0.05	W243G/W, R263K	0.05	E138E/K, R263K
	5326	V72I, I203M	0.05	S153Y, R166K/R, R263K/R	0.05	S153Y
	PNL4.3	I72V, I113V, L234V	0.05	M50I/M, V151I, R263K	0.05	M50I, V151I, R263K
	12197 Ral TI WT for INI	I203M	0.01	R263K, D288E	0.025	R263K, D288E (week 34)
AG	6399	V72I, T125A, V201I	0.025	E69E/K, G118R	0.05	G118R
	96USSN20	V72I, T125A, V201I	0.1	R263K	0.1	H51H/Y; R263K
C	4742	V72I, Q95P, T125A, V201I, I203M	0.05	G118R	0.05	H51Y, G118R
	96USNG31	V72I, T125A, V201I	0.01	S153S/T	0.025	H51Y, G139E/G
	(Mole03)	T152A, V201I				

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	5326	V72I, I203M	0.05	S153Y, R166K/R, **R263K/R**	0.05	S153Y
	PNL4.3	I72V, I113V, L234V	0.05	M50I/M, V151I, **R263K**	0.05	M50I, V151I, R263K
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AG	6399	V72I, T125A, V201I	0.025	E69E/K, G118R	0.05	G118R
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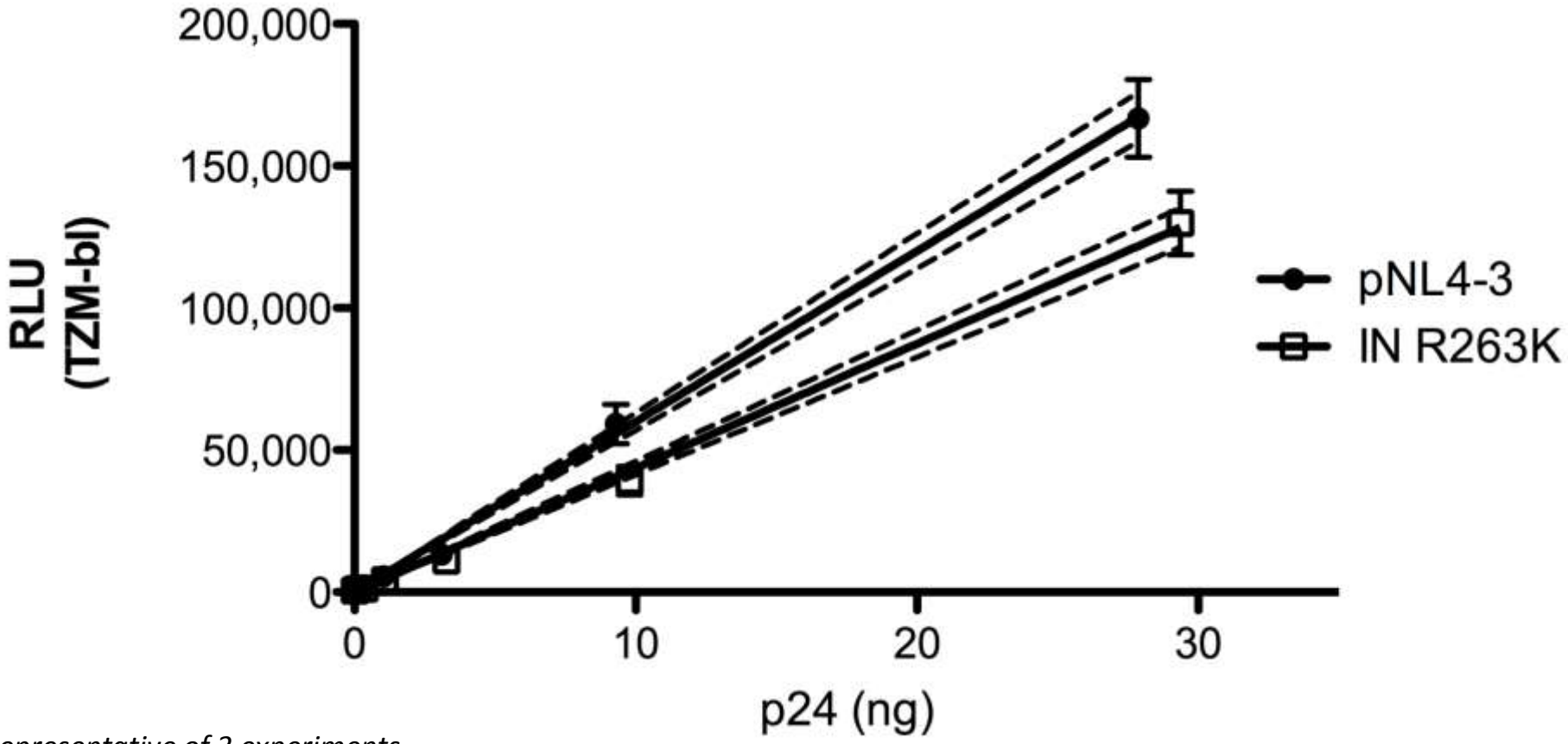
	(Mole03)	T152A, V201I				

IN mutation R263K confers resistance to DTG (TZMbl cells)

Backbone	Genotype	**DTG**	
		IC_{50} (nM)	FC
PNL4.3	wt	5.569	-
	IN_{R263K}	18.67	3.3

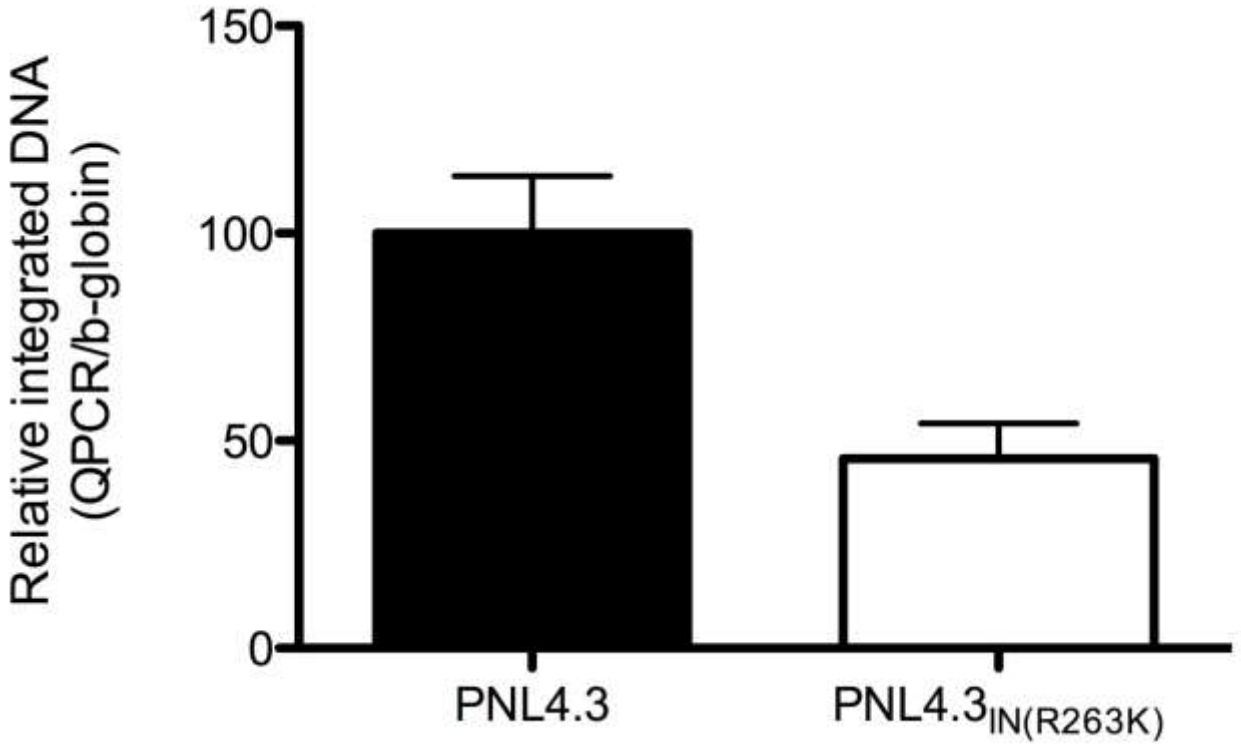
Single-round HIV1 infectivity in TZMbl

$HIV1_{IN(R263K)}$ virus infectivity 1



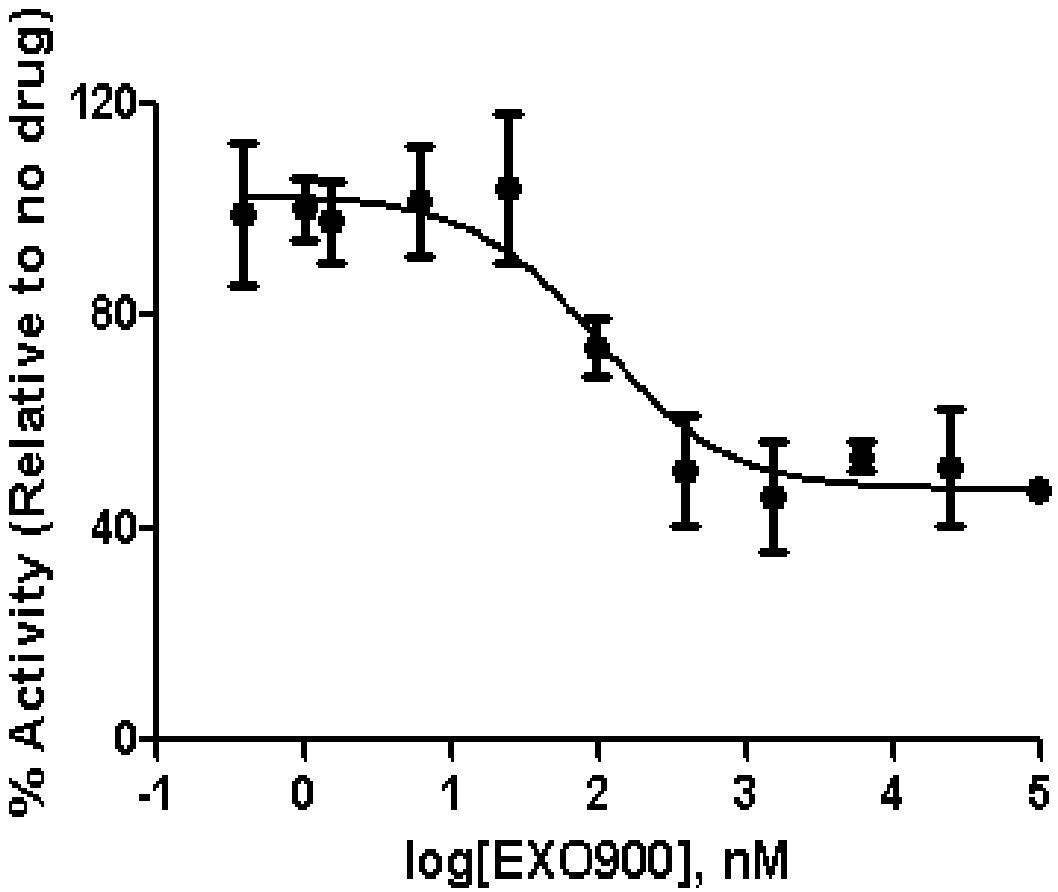
Representative of 3 experiments

Integration of the $HIV1_{IN(R263K)}$ virus after infection



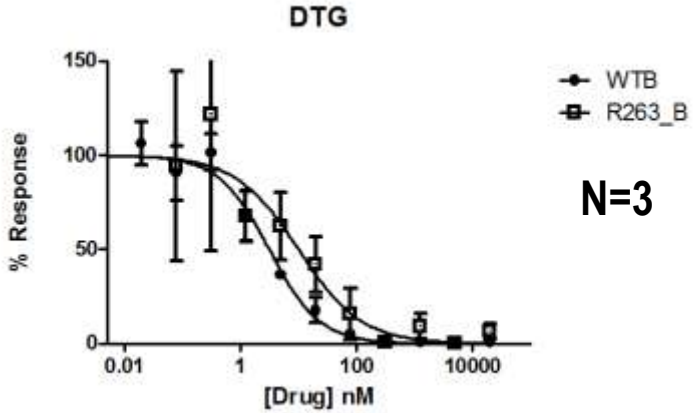
Compilation of 4 experiments with 2 sets of viruses (n=8)

Inhibition of IN WT-B 3' processing by EXO900

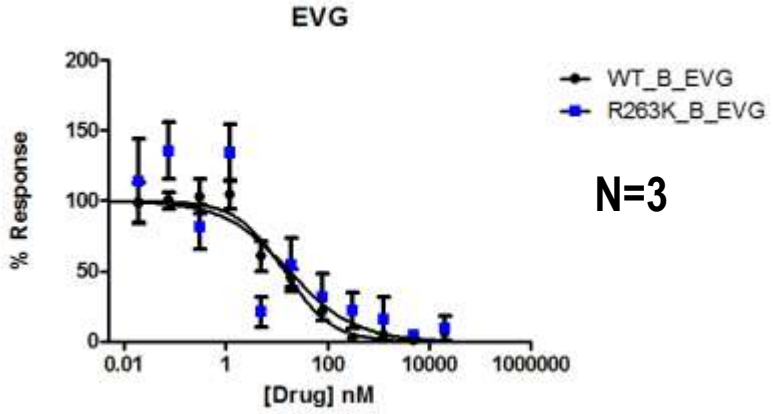


Best-fit values	
Bottom	47.13
Top	102.5
LogIC50	2.016
IC50	**103.8**
Span	55.34
Std. Error	
Bottom	3.300
Top	3.290
LogIC50	0.1835
Span	4.415
95% Confidence Intervals	
Bottom	39.52 to 54.74
Top	94.88 to 110.1
LogIC50	1.593 to 2.440
IC50	**39.20 to 275.1**
Span	45.16 to 65.52
Goodness of Fit	
Degrees of Freedom	8
R2	**0.9515**
Absolute Sum of Squares	315.1
Sy.x	6.276
Number of points	
Analyzed	11

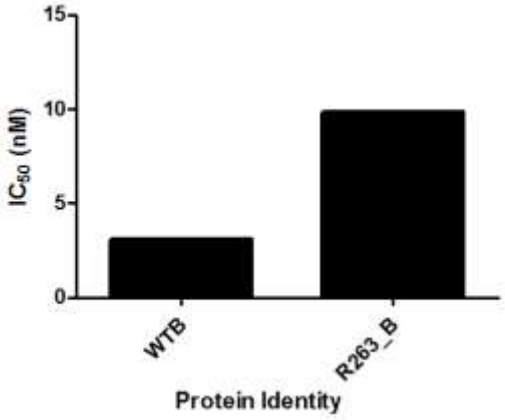
Inhibition of strand transfer

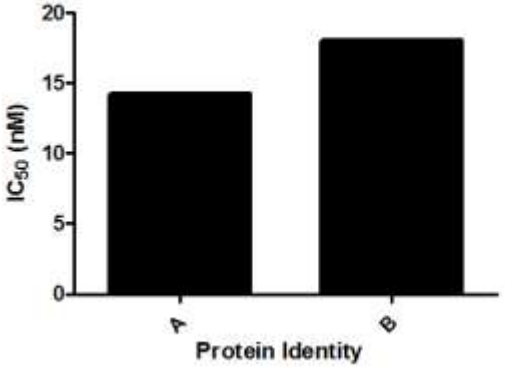


N=3



N=3





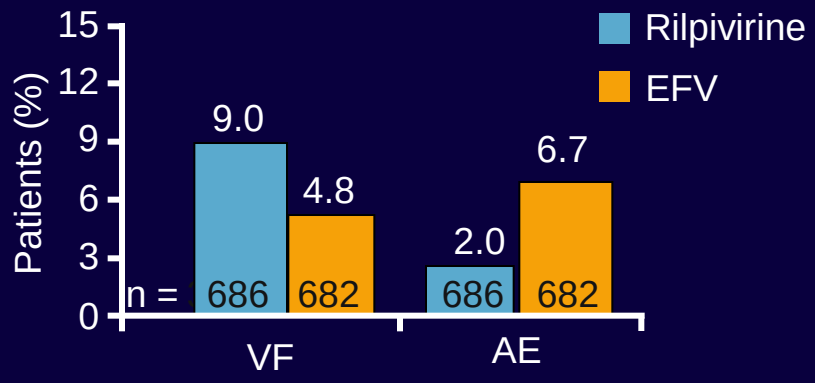
The Fitness Deficits of M184I/V in HIV Reverse Transcriptase Are Compensated by E138K that Confers Broad Cross-Resistance to Second-Generation NNRTIs.

It is well known that both the M184V and M184I mutations impair HIV replicative fitness. Previous work has shown that both the M184V and M184I enzymes are less processive than wt and that they are slower to initiate the reverse transcriptase reaction.

Recent clinical trial results conducted with rilpivirine, etravirine and GSK 2248761 (Idenix) revealed that multiple failures contained both the E138K and M184I mutations. E138K can also be selected by both etravirine and rilpivirine in tissue culture.

ECHO, THRIVE: Treatment Failure, Resistance, and Adverse Events

Treatment Failure in ECHO and THRIVE



Resistance at Virologic Failure

Wk 48 Outcome	Rilpivirine (n = 686)	Efavirenz (n = 682)
VF with resistance data, n	62	28
No NNRTI or NRTI RAMs,%	29	43
≥ 1 Emergent NNRTI RAM,%	63	54
▪ Most frequent NNRTI RAM	E138K	K103N
≥ 1 Emergent NRTI RAMs, %	68	32
▪ Most frequent NRTI RAM	M184I	M184V

Adverse Events and Discontinuation

Wk 48 Outcome, %	Rilpivirine (n = 686)	Efavirenz (n = 682)	*P* Value
DC for AE	3	8	.0005
Most Common AEs of Interest, %			
Any neurologic AE	17	38	< .0001
Any psychiatric AE	15	23	.0002
Any rash	3	14	< .0001

Cohen C, et al. AIDS 2010. Abstract THLBB206. Table used with permission.

M184I vs M184V

M184I usually arises first because it derives from the G to A hypermutation.

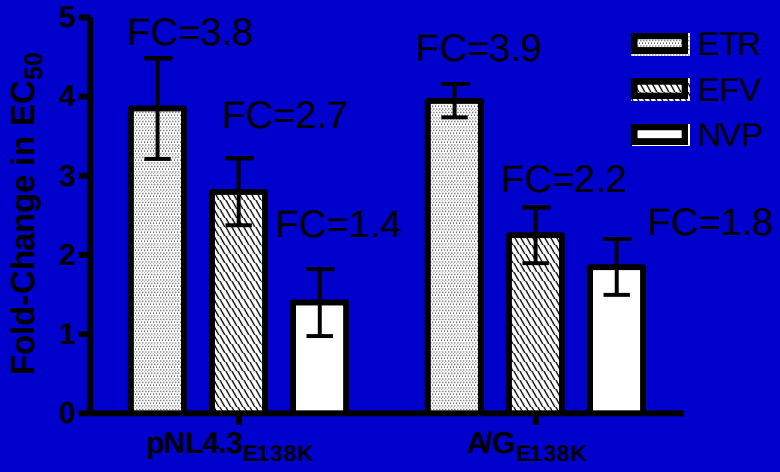
ATG ➡ ATA

M184V subsequently arises due to an independent substitution within the same triplet codon.

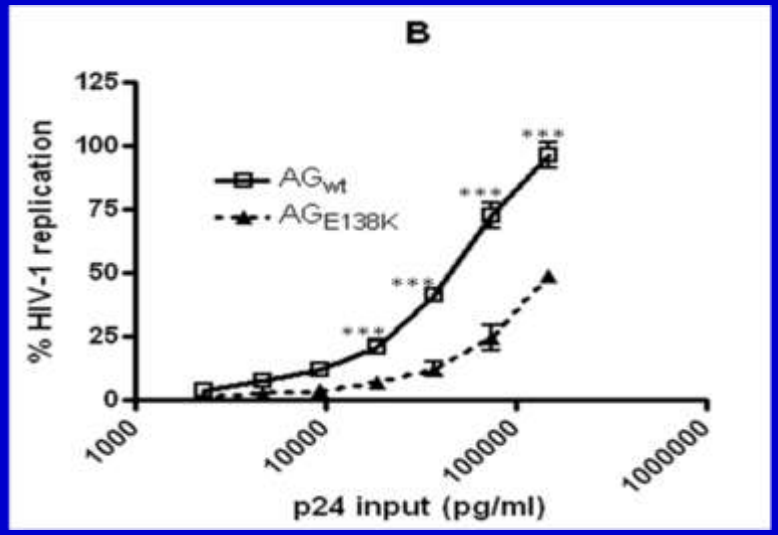
ATG ➡ GTG

Then, M184V out-competes M184I because of superior replicative capacity.

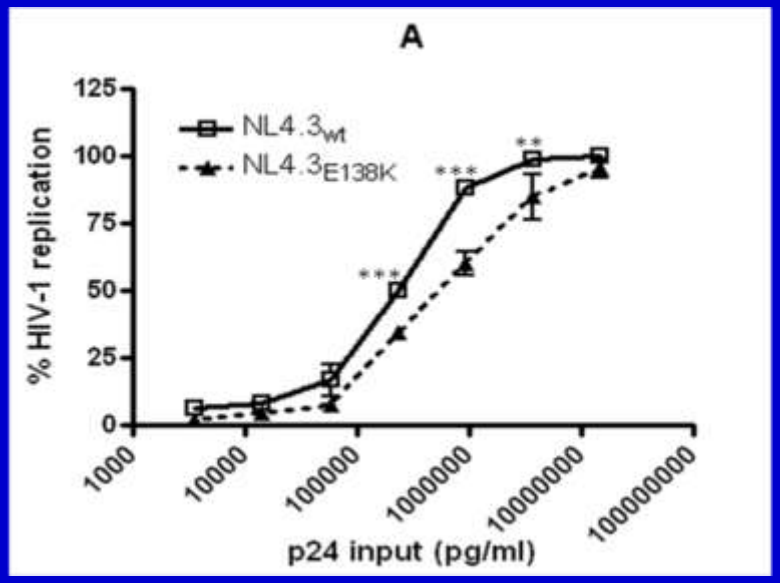
Impact of E138K in recombinant HIV-$1_{NL-4.3}$ and HIV-1_{AG} viruses on NNRTIs susceptibility and replication capacity (RC)



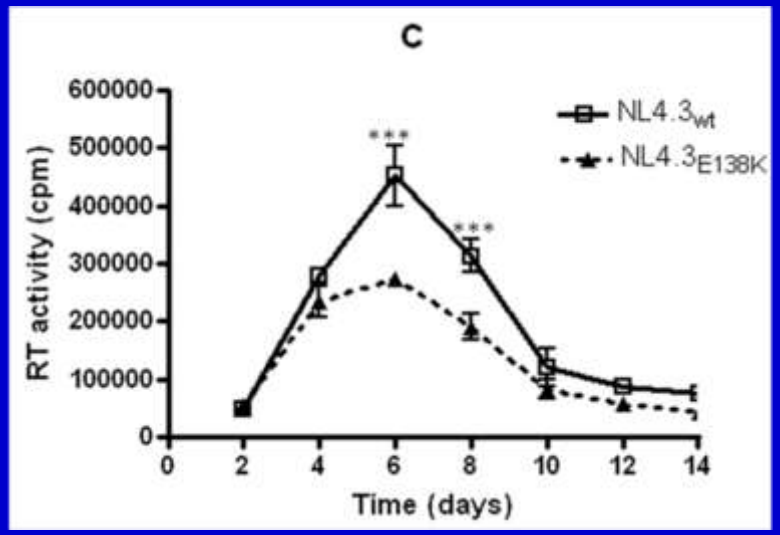
B: RC in TZM-bl after 48 hrs



A: RC in TZM-bl after 48 hrs



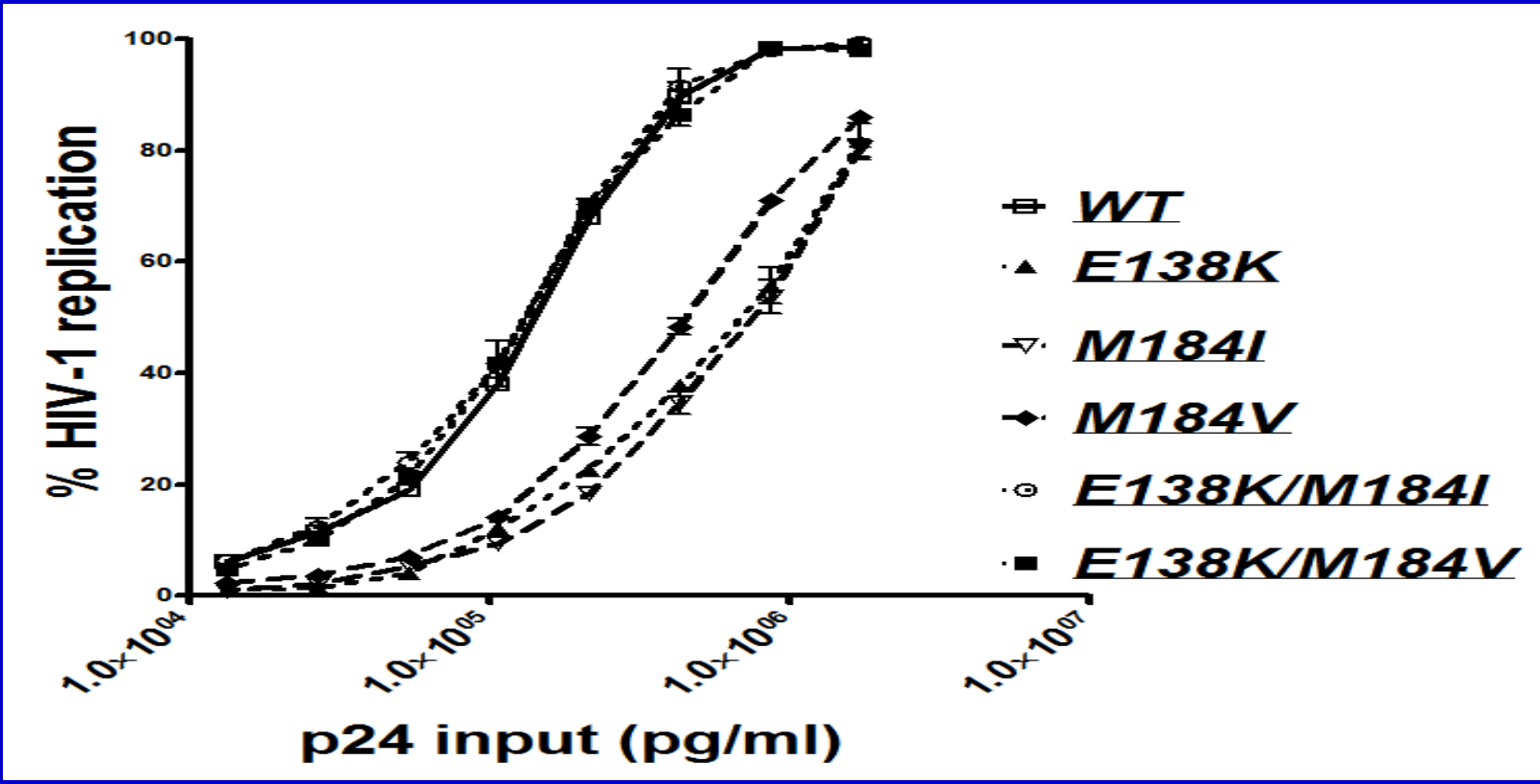
C: Growth curve in CBMCs after 14 days



The RC of E138K was impaired by 2 to 3-fold compared to WT.

Asahchop et al. AAC 2011; 55:600-7.

Compensatory effect of E138K on the replication capacity (RC) of M184I/V.



✓The RC of both E138K and M184I are each decreased by 3-fold compared to wild-type and decreased by 2-fold for M184V.

✓There is no difference in RC of double mutants E138K/M184I or E138K/M184Vc compared to wild-type .

Conclusions

1. The HIV-1 RT E138K mutation has the potential to be an important signature mutation for the second-generation NNRTIs ETR and RPV.

2. The E138K mutation restores RT enzymatic processivity and the viral replication capacity of HIV-1 variants harboring M184I/V.

3. In the ECHO and Thrive clinical trials, we believe that the presence of E138K stabilized viruses containing M184I, thus obviating the need for HIV to develop M184V.

4. This compensatory effect of E138K for M184I/V may have clinical significance in regard to treatment failures involving ETR and other novel NNRTIs as well as on the detectability of these mutations in transmitted resistance.

Acknowledgements

- Hongtao Xu
- Thibault Mesplede
- Peter Quashie
- Maureen Oliveira
- Eugene Asahchop
- Ying-Shan Han
- Mark Underwood, GSK
- Tamio Fujiwara, Shionogi