Two-drug combination passage among dolutegravir, rilpivirine, elvitegravir and Lamivudine

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Background

- A two-drug regimen may provide an option for less adverse events and reduced administrative burden; however, durable virologic suppression and the risk for emergence of drug resistant virus is of concern.

- Recently, results of LATTE study as two-drug oral maintenance therapy of INSTI, cabotegravir (CAB) + NNRTI, rilpivirine (RPV)has demonstrated non-inferiority to the preferred 3-drug regimen through 96 weeks. (CROI 2015, poster554LB).
- Regimen switch study to INSTI, dolutegravir (DTG) + RPV from current antiretroviral regimen (SWORD-1,2) are ongoing.
- In this study, *in vitro* passage studies of two-drug combinations were conducted to investigate viral growth and drug resistance emergence pattern by passaging under 2-drug combination compared with that of under a single drug.

Materials and Methods in a concentration constant method

Virus and cell: NL432 and MT-2

Drugs: single : RPV, 3TC, EVG, DTG

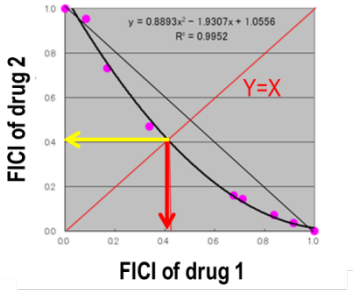
combination : RPV + DTG, 3TC + DTG, RPV + 3TC, RPV + EVG, 3TC + EVG

Drug concentration:

single: 0.5, 1, 2, 4, 8, 16, 32, 64x EC50* for RPV, EVG, DTG

0.5, 1, 2, 64, 320, 640x EC50* for 3TC

combination: 1, 2, 4, 8, 16x cEC50# for each drug in the combination



#Combination EC50 $_{Dn}$ (cEC50$_{Dn}$) = EC50$_{Dn}$ x Fractional Inhibitory Concentration Index (FICI), where FICI of drug 1 is equal to FICI of drug 2 for each drug combination. (n= 1 or 2)

Passage condition: Passage under constant drug concentrations through 85 days

*EC50(nM)

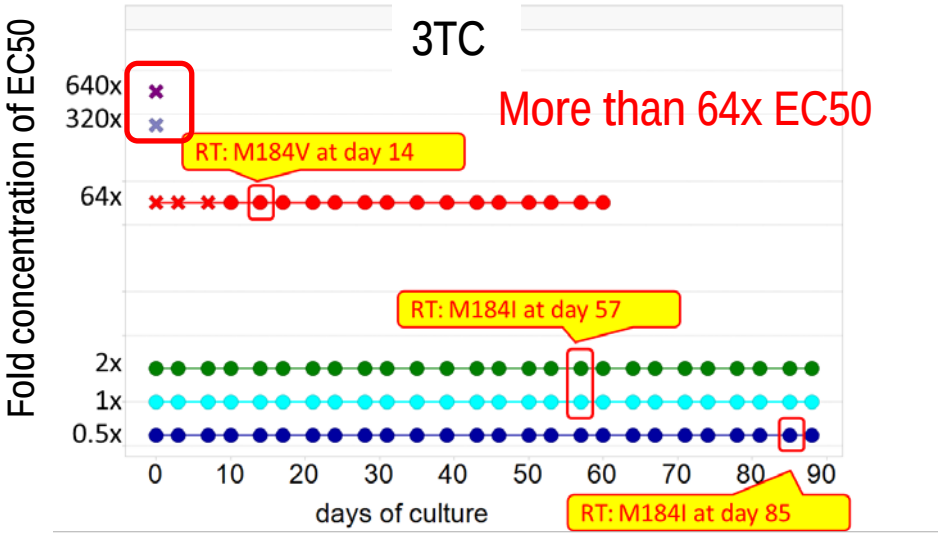
drug	EC50 nM	EC90 nM
3TC (Lamivudine)	3310	9055
RPV (Rilpivirine)	1.2	2.6
DTG (Dolutegravir)	2.1	5.3
EVG (Elvitegravir)	1.4	4.4

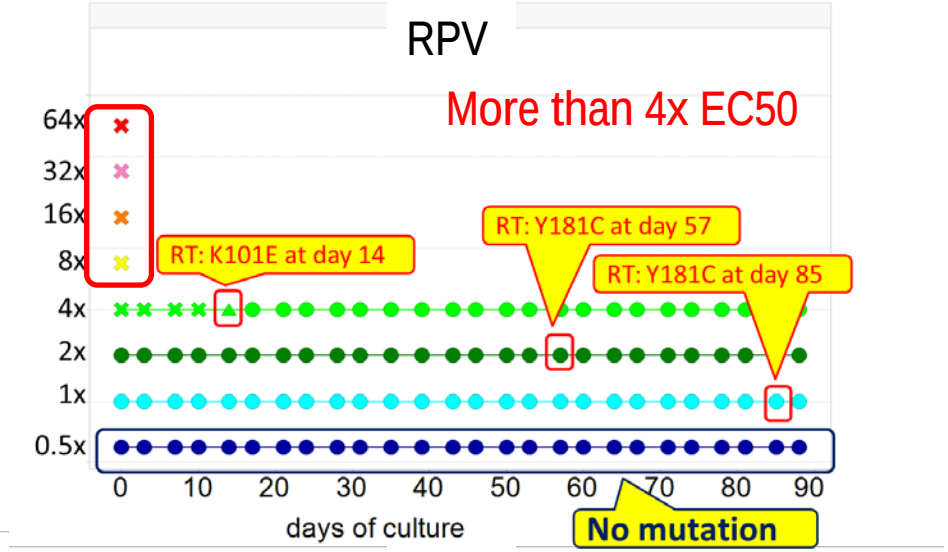
cEC50 is roughly equal to ½ x EC50.

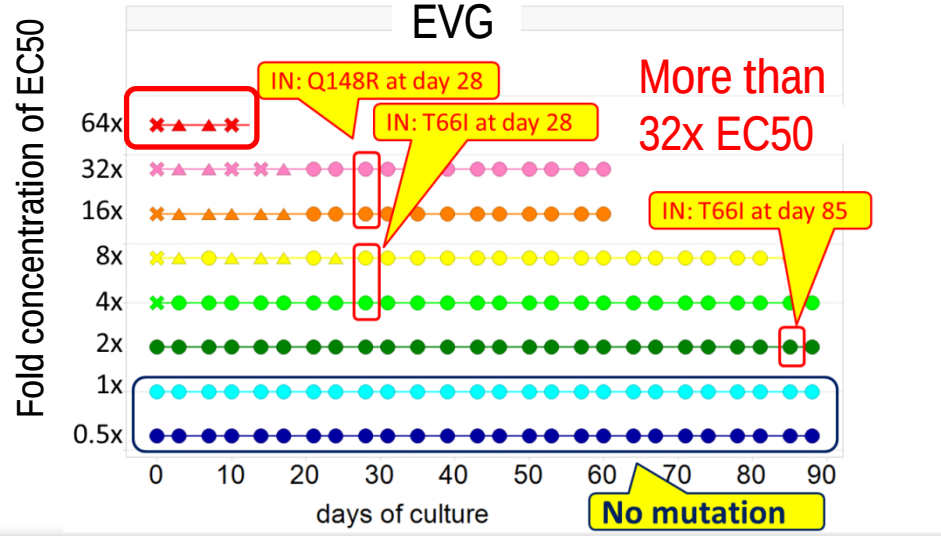
#cEC50(nM) of each drug in the combination

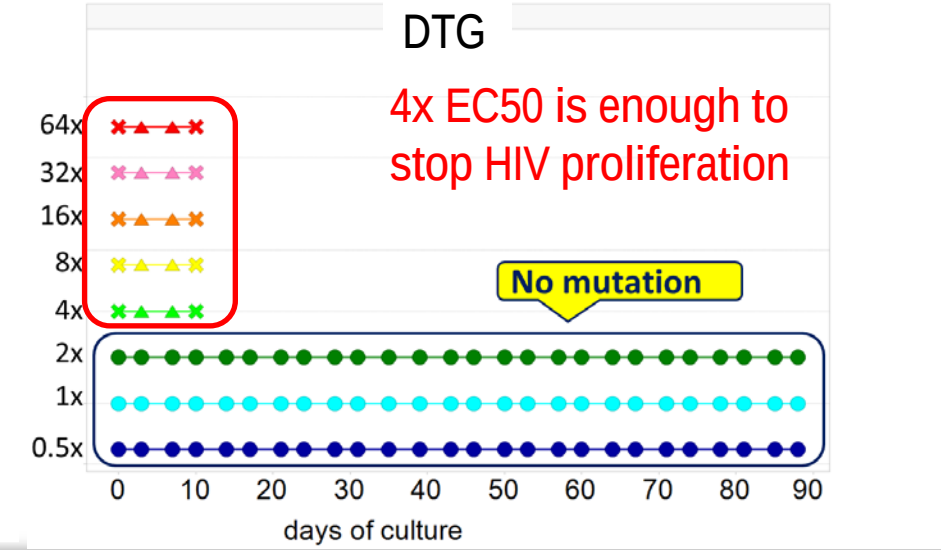
D1 + D2	FICI	cEC50 D1 nM	cEC50 D2 nM
EVG + 3TC	0.431	0.60	1426
DTG + 3TC	0.428	0.89	1416
EVG + RPV	0.509	0.71	0.63
DTG + RPV	0.489	1.0	0.60
RPV + RPV	0.4999	0.62	0.62
3TC + RPV	0.452	1496	0.56

Passage results of single compounds



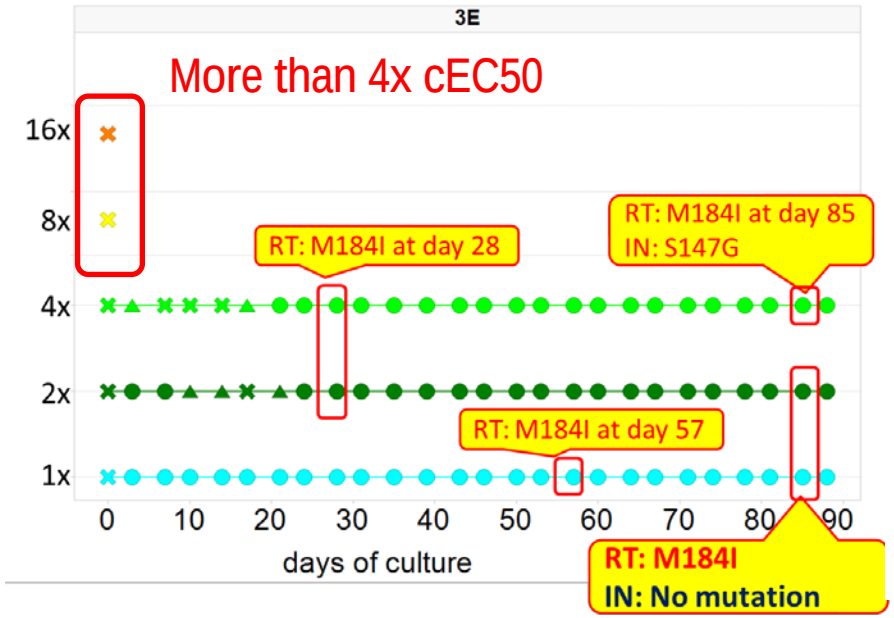




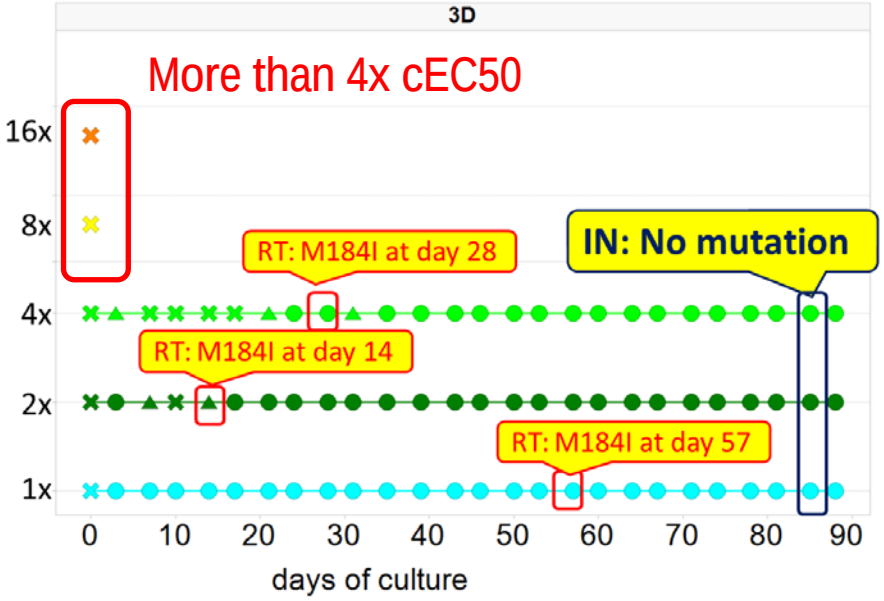


Passage results of combination with 3TC

A) 3TC+EVG



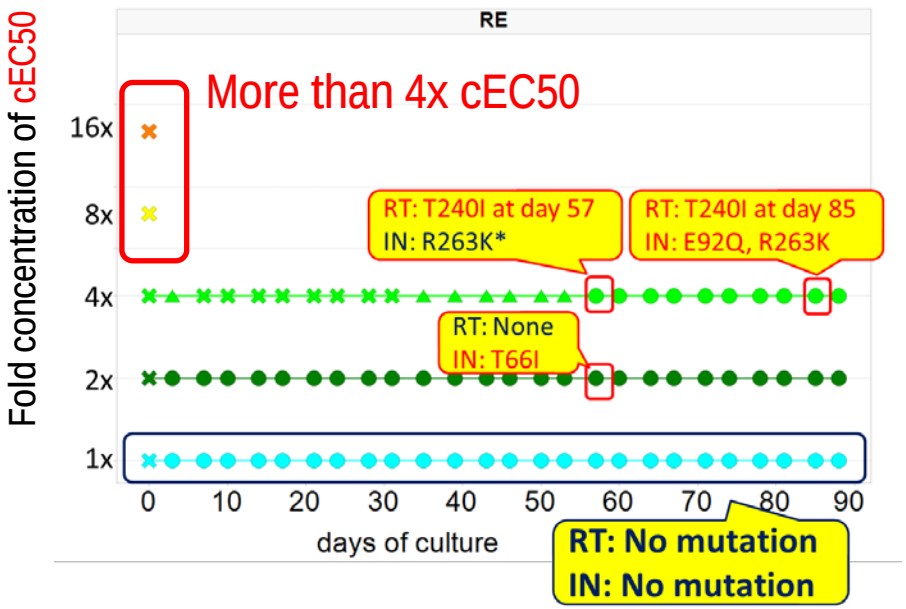
B) 3TC+DTG



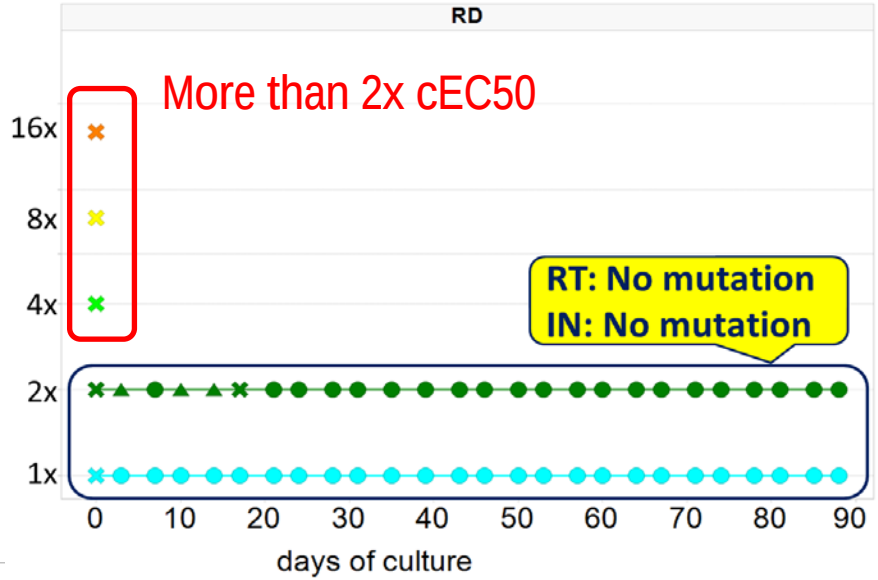
- Both combination could stop HIV proliferation at more than 4x cEC50.
- No INSTI resistant virus emerged in the combination of 3TC and DTG.

Passage results of combination with RPV

A) RPV+EVG



B) RPV+DTG



* FC of R263K against EVG is 1.3.

- Neither NNRTI nor INSTI resistant virus emerged in the combination of RPV and DTG.

Summary Results of Concentration Constant Method

Single drug

Fold concentration of EC50

	3TC	RPV	EVG[1)]	DTG
320x		ND	ND	ND
64x	14			
32x	ND		28	
16x	ND		28	
8x	ND		14*	
4x	ND	14	14*	
2x	57	57	85	
1x	57	85		
0.5x	85			

No replication

Resistant virus emerged (the first day when a primary resistant virus was isolated)

Replicated without resistant mutation

ND: No data

1) Q148R was isolated in a well, however T66I emerged at day 14 in another well (*data not shown).

DTG: 8.4nM > 4.0nM

RPV: 9.6nM > 2.4nM

2-drug combination

Fold concentration of cEC50

	3TC+RPV		3TC+DTG		3TC+EVG		RPV+DTG		RPV+EVG	
	RT	RT	RT	IN	RT	IN	RT	IN	RT	IN
16x										
8x										
4x	28	57	28		28	85			57	85
2x	28		14		28					57
1x			57		57					

Combination of RPV and DTG is the best among those investigated in this study.

Summary Results of Concentration Stepwise Increasing Method

Fold concentration of cEC50

	3TC+RPV		3TC+DTG		3TC+EVG		RPV+DTG		RPV+EVG	
	RT	RT	RT	IN	RT	IN	RT	IN	RT	IN
1024x	ND	ND	ND	ND			ND	ND	ND	ND
512x	ND	ND	ND	ND			ND	ND	ND	ND
256x	ND	ND	ND	ND			ND	ND	ND	ND
128x			ND	ND			ND	ND	ND	ND
64x			ND	ND		57(4x)	ND	ND	ND	ND
32x		57(4x)				57(2X)	ND	ND		
16x		57(1x, 2x)		*		57(1x)				85(1x, 4x)
8x	28(2x)		28(2x)		28(1x, 4x)				57(2x, 4x)	57(2x)
4x	28(1x)		28(1x, 4x)		28(1x, 2x)		57(1x),85(2x)		85(1x),57(1x,4x)	57(4x)
2x			14(2x)		14(2x)					57(1x)
1x										

* IN/R263K emerged at day 85 after RT/M184I emerged at day 14. FC of R263K against DTG is 1.5.

No replication

Resistant virus proliferated at 85 days

The first day when a primary resistant virus isolated is indicated (culture starting concentration)

Replicated without resistant mutation

ND: No data

Culture starting concentration

- Combination of RPV and DTG is the best in concentration stepwise increasing method also.

Conclusions & Discussion

- Two-drug combination could stop HIV proliferation at lower concentration than single drug.
- Combination of RPV and DTG is the best among those investigated in this study because neither NNRTI nor INSTI resistant virus emerged and because HIV could not replicate at the lowest concentration.

	Single	=>	two-drug
RPV:	8xEC50(9.6nM)		4xcEC50(2.4nM)
DTG:	4xEC50(8.4nM)		4xcEC50(4.0nM)

- Concentration stepwise increasing method showed the similar results as the constant concentration method with
  - Resistant virus emerged timing is the same as that with the highest drug concentration condition in the constant concentration method.
  - Combination of RPV+DTG could stop HIV proliferation at the lowest concentration among combinations investigated in this method although RT/E138K or Y181C emerged.