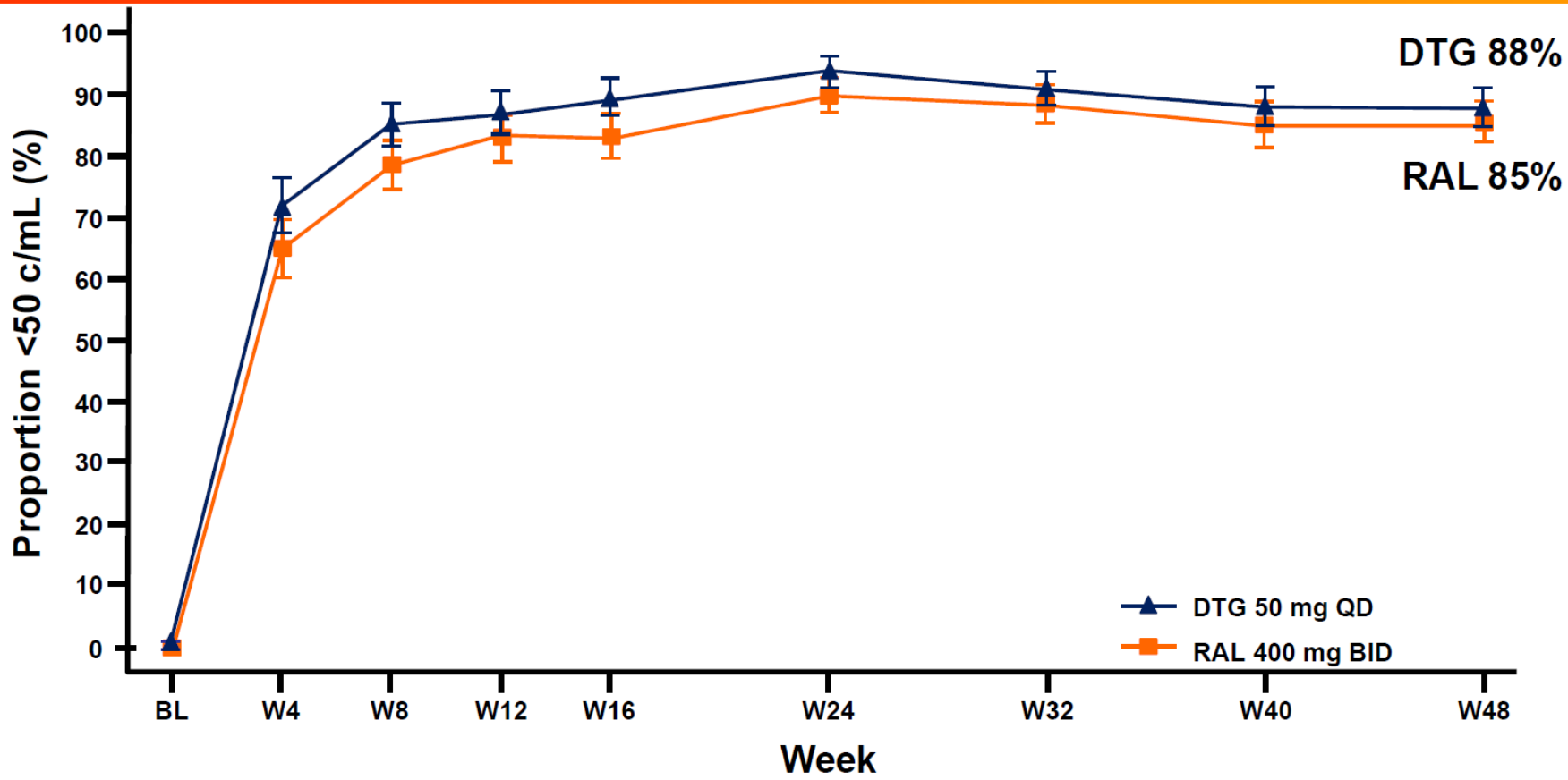
What if a Drug that Was Developed to Treat HIV Infection Could Actually Help to Cure It?

Mark A Wainberg
McGill University AIDS Centre
Jewish General Hospital
Montreal, Quebec, Canada

Virologic Success Over Time

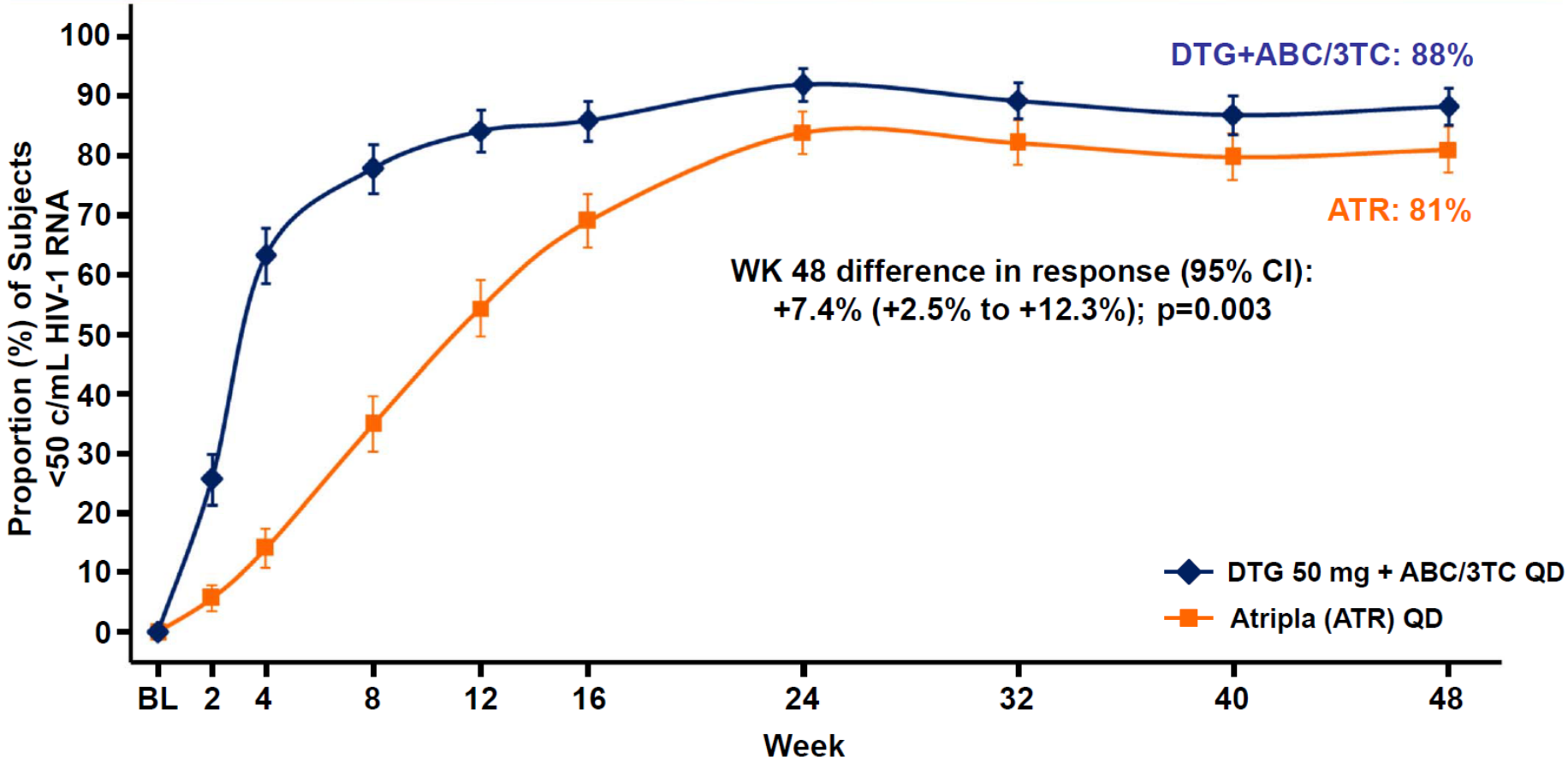


Median (IQR) Change From Baseline $CD4^+$ Cell Count ($cells/mm^3$)

	W4		W24		W48	
DTG 50 mg QD	87	(26, 149)	183	(100, 295)	230	(128, 338)
RAL 400 mg BID	88	(32, 163)	182	(94, 296)	230	(139, 354)

Raffi F, et al. Lancet 2013, Janv 8 (epub)

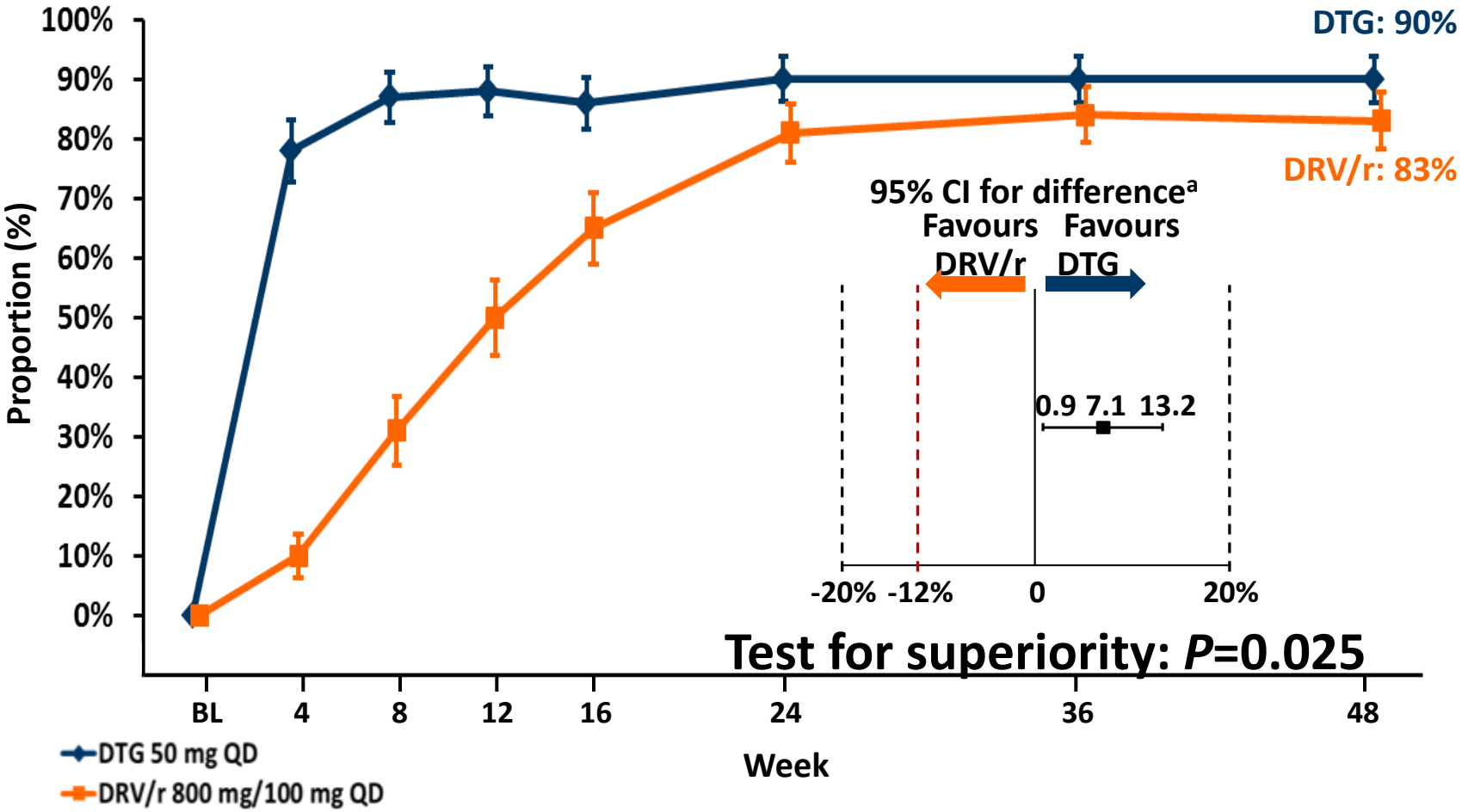
Proportion (95% CI) of Subjects <50 c/mL (FDA Snapshot)



- DTG 50mg +ABC/3TC QD was statistically superior to Atripla at Week 48 (primary endpoint)
- Subjects receiving DTG +ABC/3TC achieved virologic suppression faster than Atripla, median time to HIV-1 RNA <50c/mL of 28 days (DTG +ABC/3TC) vs 84 days (Atripla), P<0.0001

Walmsley S, ICAAC 2012, Abst. H-556b

Proportion (95% CI) of Individuals With HIV-1 RNA <50 c/mL Over Time – Snapshot



Results were confirmed in per protocol analysis: 91% DTG versus 84% DRV/r, Δ (CI): 7.4 (1.4 - 13.3)

Clotet et al. EACS 2013; Brussels, Belgium. Abstract LBPS4/6.

IN VITRO, MOST RAL- AND EVG-RESISTANT SINGLE MUTANTS ARE SUSCEPTIBLE TO DTG

Viruses	Mean FC DTG	RAL	EVG
WT[1,2]	1	1	1
T66A[1,2]	0.26	0.61	4.1
T66I[1,2]	0.26	0.51	8.0
T66K[1,2]	2.3	9.6	84
E92I[1,2]	1.5	2.1	8.0
E92Q[1,2]	1.6	3.5	19
E92V[1,2]	1.3	1.4	8.3
G118S[1,2]	1.1	1.2	4.9
F121Y[1,2]	0.81	6.1	36
T124A[1,2]	0.95	0.82	1.2
E138K[1,2]	0.97	1	0.93
G140S[1,2]	0.86	1.1	2.7
Y143C[1,2]	0.95	3.2	1.5
Y143H[1,2]	0.89	1.8	1.5

Viruses	Mean FC DTG	RAL	EVG
Y143R[1,2]	1.4	16	1.8
P145S[1,2]	0.49	0.87	>350
Q146R[1,2]	1.6	1.2	2.8
Q148H[1,2]	0.97	13	7.3
Q148K[1,2]	1.1	83	>1700
Q148R[1,2]	1.2	47	240
I151L[1,2]	3.6	8.4	29
S153F[1,2]	1.6	1.3	2.8
S153Y[1,2]	2.5	1.3	2.3
M154I[1,2]	0.93	0.82	1.1
N155H[1,2]	1.2	11	25
N155S[1,2]	1.4	6.2	68
N155T[1,2]	1.9	5.2	39
G193E[2]	1.3	1.3	1.3

3 ≤ FC < 5 5 ≤ FC < 10 ≤ FC

RAL and EVG-related single mutation IDMs (site directed mutants)
DTG, dolutegravir; FC, fold change

1. Adapted from Kobayashi M, et al. Antimicrob Agents Chemother 2011;55:813–21
2. Adapted from Seki T, et al. CROI 2010. Abstract 555

IN VITRO, MOST RAL- AND EVG-RESISTANT MULTIPLE MUTANTS ARE SUSCEPTIBLE TO DTG

Viruses	Mean FC DTG	RAL	EVG
WT	1	1	1
T66I/L74M	0.35	2.0	14
T66I/E92Q	1.2	18	190
T66K/L74M	3.5	40	120
L74M/N155H	0.91	28	42
E92Q/N155H	2.5	>130	320
T97A/N155H	1.1	26	37
L101I/S153F	2.0	1.3	2.6
F121Y/T125K	0.98	11	34
E138A/Q148R	2.6	110	260
E138K/Q148H	0.89	17	6.7
E138K/Q148K	19	330	371
E138K/Q148R	4.0	110	460

Viruses	Mean FC DTG	RAL	EVG
G140C/Q148R	4.9	200	485
G140S/Q148H	2.6	>130	>890
G140S/Q148K	1.5	3.7	94
G140S/Q148R	8.4	200	267
Y143H/N155H	1.7	38	16
Q148R/N155H	10	>140	390
N155H/G163K	1.4	23	35
N155H/G163R	1.1	17	35
N155H/D232N	1.4	20	36
V72I/F121Y/T125K	1.3	13	58
L101I/T124A/S153F	1.9	1.4	2.0
E138A/S147G/Q148R	1.9	27	130
V72I/F121Y/T125K/I151V	1.2	7.0	37

3 ≤ FC < 5 5 ≤ FC < 10 10 ≤ FC

RAL and EVG-related single mutation SDMs (site directed mutants)
WT, wild type

Adapted from Kobayashi M, et al. Antimicrob Agents Chemother 2011;55:813–21

Subtype-specific mutations selected *in vitro* with dolutegravir

HIV-1 subtype	Most common mutations selected with dolutegravir
B	R263K, H51Y
C	G118R, H51Y

Quashie, Mesplède et al., Journal of Virology, 2012

The R263K mutation confers low-level resistance to dolutegravir in cell culture

Genotype	**IC_{50} fold change***
R263K	2.5 to 6

**Methodological differences*
(EC_{50} for wild-type ≈1-6nM)

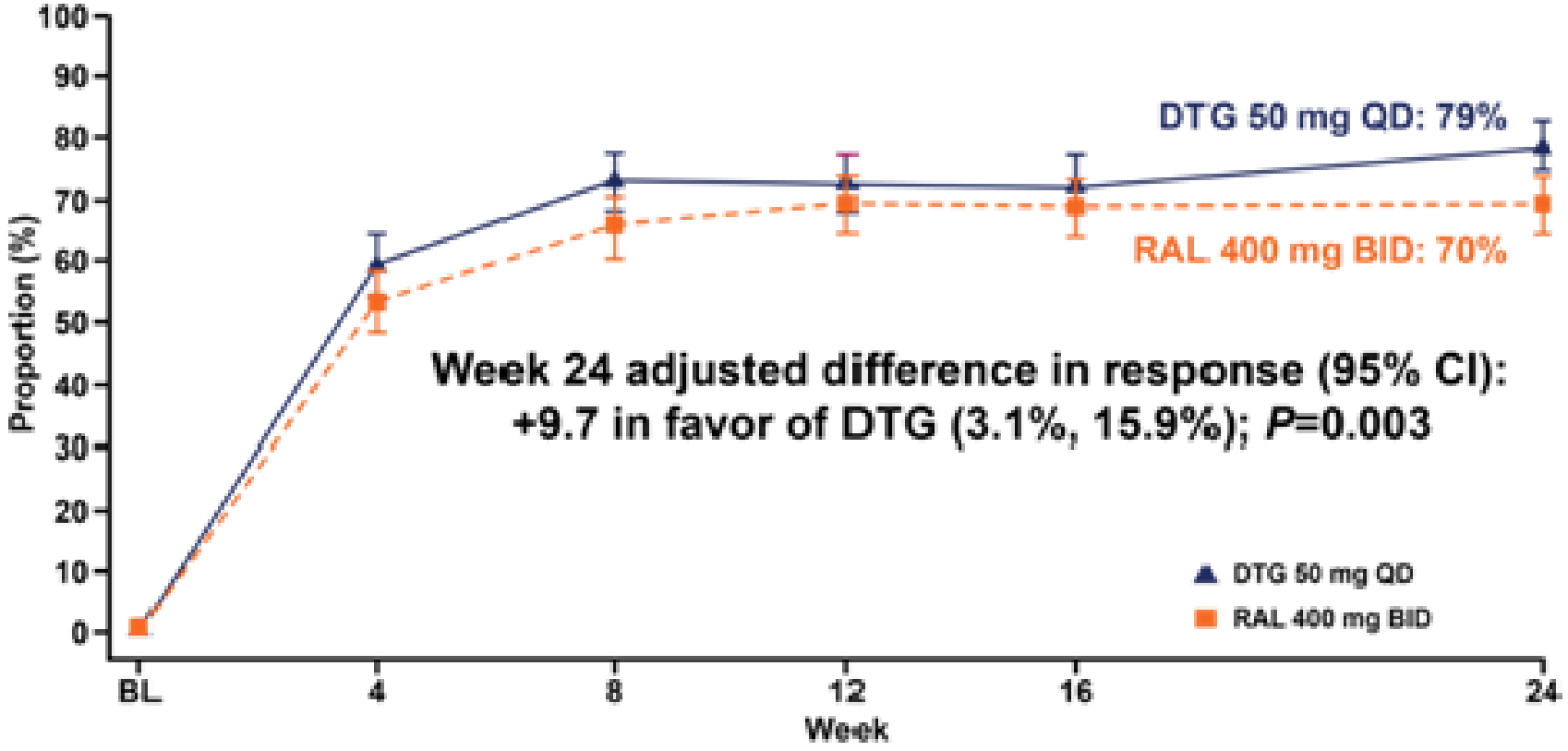
Quashie, Mesplède et al., Journal of Virology, 2012

SAILING

- CROI 2013. A study in which Dolutegravir was shown to be superior to Raltegravir in treatment-experienced integrase inhibitor-naïve subjects.
- The R263K mutation was present in two individuals who either rebounded or did not achieve virologic suppression to <50 c/ml.

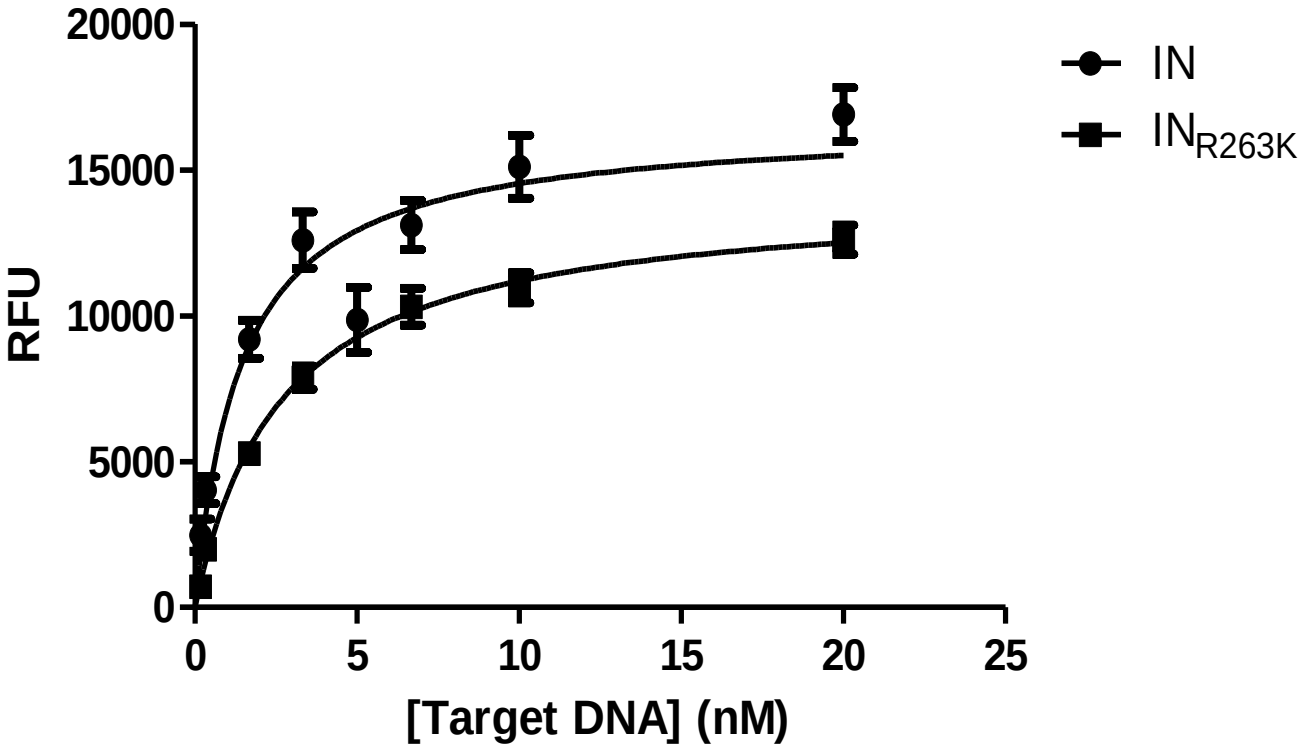
Figure 2. Proportion of Subjects With HIV-1 RNA <50 c/mL (Snapshot, mITT-E)

DTG 50 mg QD was statistically superior to RAL 400 mg BID at Week 24.



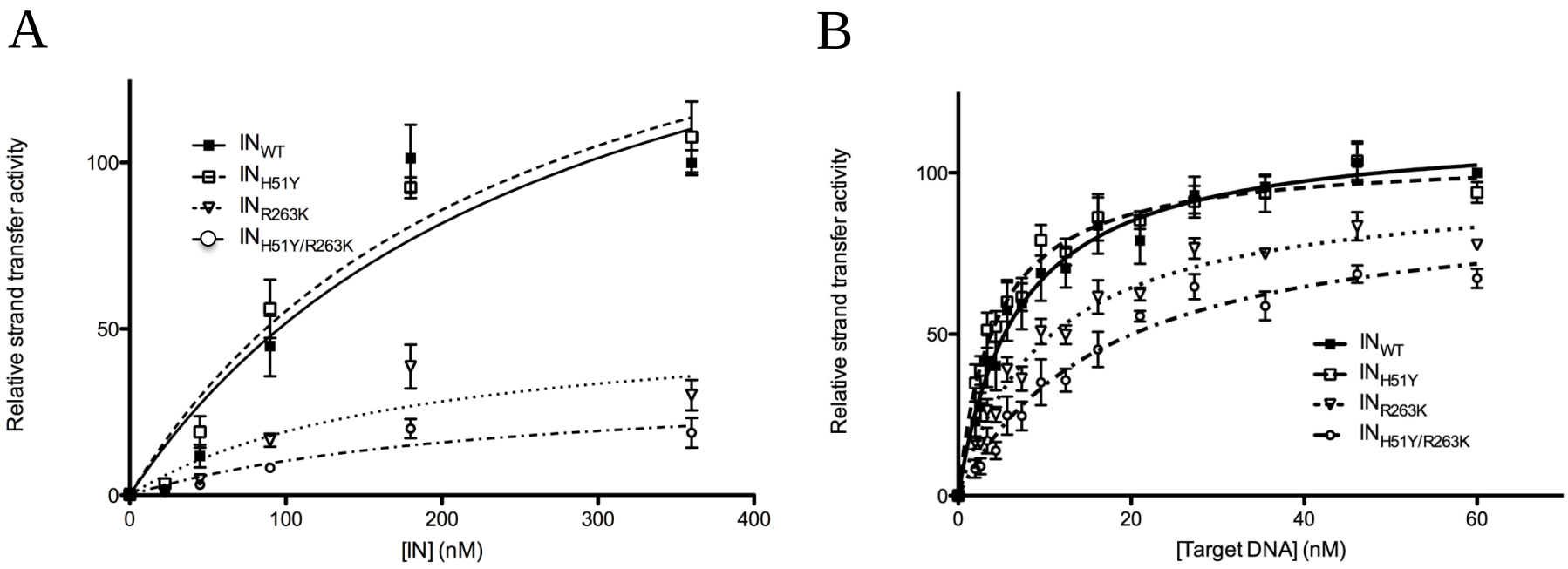
*Adjusted difference based on stratified analysis adjusting for Baseline HIV-1 RNA (≤50,000 c/mL vs >50,000 c/mL), DRV/r use without primary PI mutations and Baseline PSS (2 vs <2)

The R263K mutation decreases integrase activity in cell-free assays

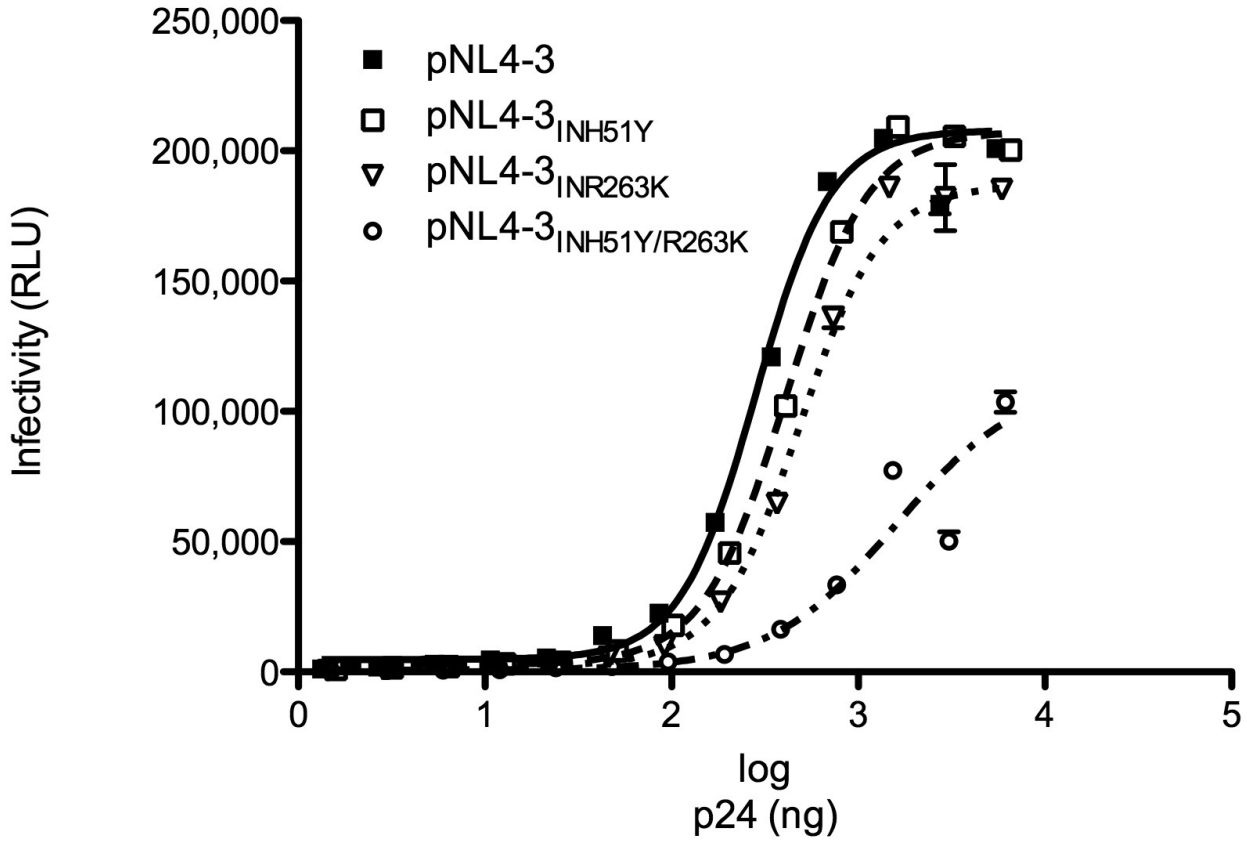


Quashie, Mesplède et al., Journal of Virology, 2012

The addition of H51Y to R263K further decreases IN strand transfer activity



The combination of H51Y and R263K negatively impacts viral fitness



Selection of DTG-Resistant Viruses with 3TC

Virus	Weeks 8-15
WT	M184V
H51Y	M184I
R263K	M184I
H51Y/R263K	**None**
G118R	**None**
H51Y/G118R	**None**

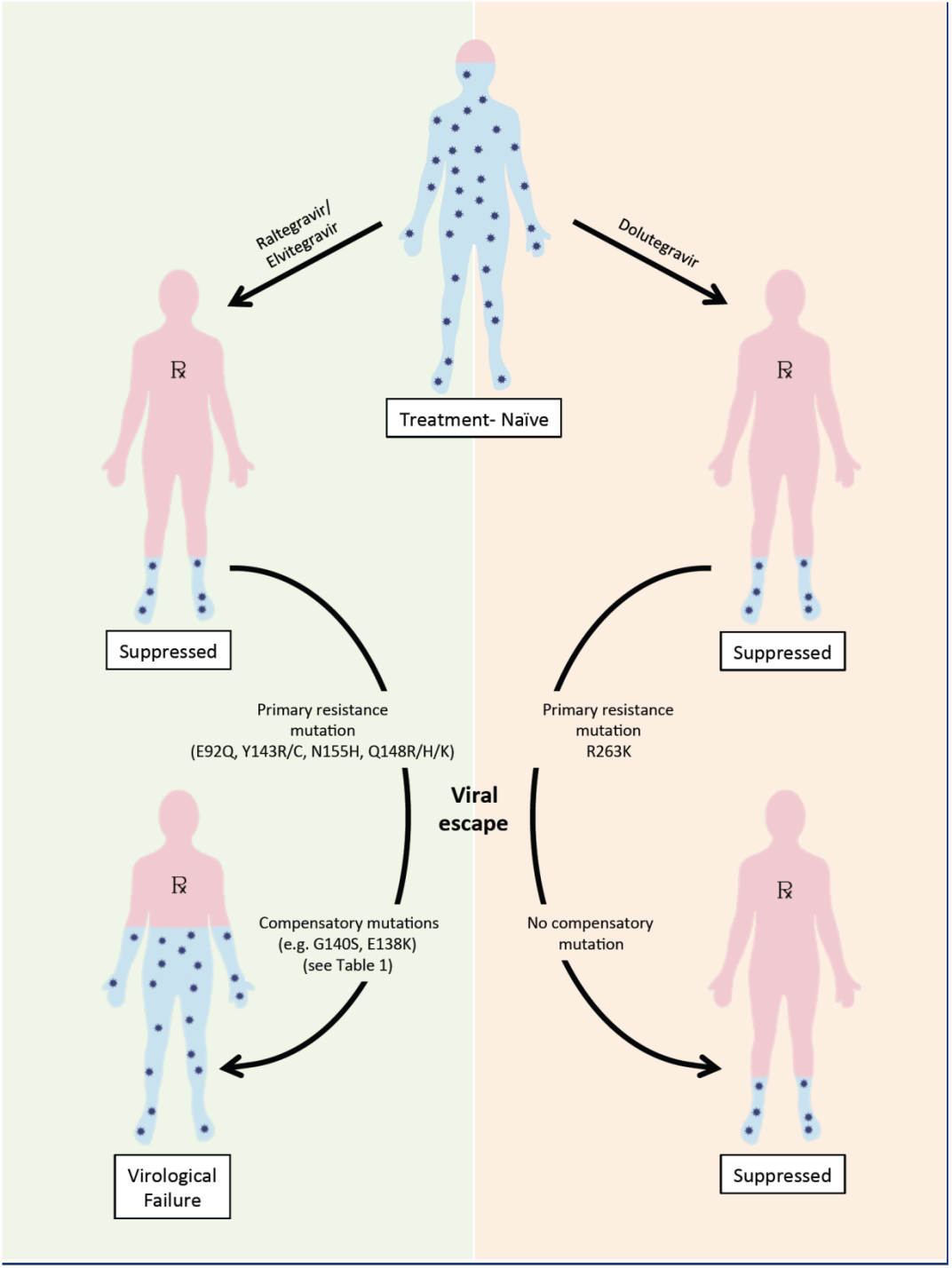
The R263K Mutation Confers a Higher Level of Drug Resistance against DTG than INSTI Mutations Associated with RAL and EVG

Mutations at positions	Fold resistance to		
	RAL	EVG	DTG
E92Q	2-3.5	15-20	<2
Y143	3-16	1.5-2	<1.5
Q148	10-50	10-100	<1.2
N155H	5-15	25-50	<1.2
R263K	<1	2-4	4-5

This explains why R263K is selected preferentially by DTG and why the R263K virus is then unable to proceed along any of the alternative INSTI resistance pathways that are associated with high level resistance against all members of the INSTI family of drugs

Replication Capacity of HIV Containing Various Combinations of INSTI Resistance Mutations

Mutation(s)	% fitness
E92Q	≈ 75%
Y143	≈ 72%
Q148	≈ 75%
N155	≈ 75%
R263K	≈ 70%
G140/Q148	≈ 95%
R263K/H51Y	≈ 25%
R263K/E138K	≈ 25%


Raltegravir/
Elvitegravir
Dolutegravir
Treatment- Naïve
Suppressed
Suppressed
Primary resistance
mutation
(E92Q, Y143R/C, N155H, Q148R/H/K)
Primary resistance
mutation
R263K
Viral
escape
Compensatory mutations
(e.g. G140S, E138K)
(see Table 1)
No compensatory
mutation
Virological
Failure
Suppressed

Hypotheses

1. Viruses resistant to DTG via the R263K pathway should not be transmissible because of low viral fitness
2. A series of judicious treatment interruptions followed by the use of DTG could conceivably convert viruses that are archived into attenuated forms.

No compensatory mutations in regard to DTG resistance and viral fitness have developed over more than three years in culture.

Conclusions

- Resistance mutations selected in vitro with dolutegravir are: R263K or G118R plus H51Y
- R263K and G118R confer low-level resistance against dolutegravir, e.g. 2.5-6 fold
- The addition of H51Y to either R263K or G118R increases resistance against DTG but also further decreases viral fitness
- These findings help to explain why resistance against dolutegravir in INSTI-naïve patients has not been observed

Acknowledgements

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Thanks to CIHR and CANFAR

Dolutegravir activity on RAL-resistant clinical isolates (n=39)

(median IC_{50} for wild-type=1.07 nM)

Genotype	Median fold change
N155H	1.37
Y143R/T97A	1.05
Q148H/G140S	3.75
Q148R/G140S	13.3

Underwood et al., JAIDS, 2012