Not All Drug Regimens Are Created Equal

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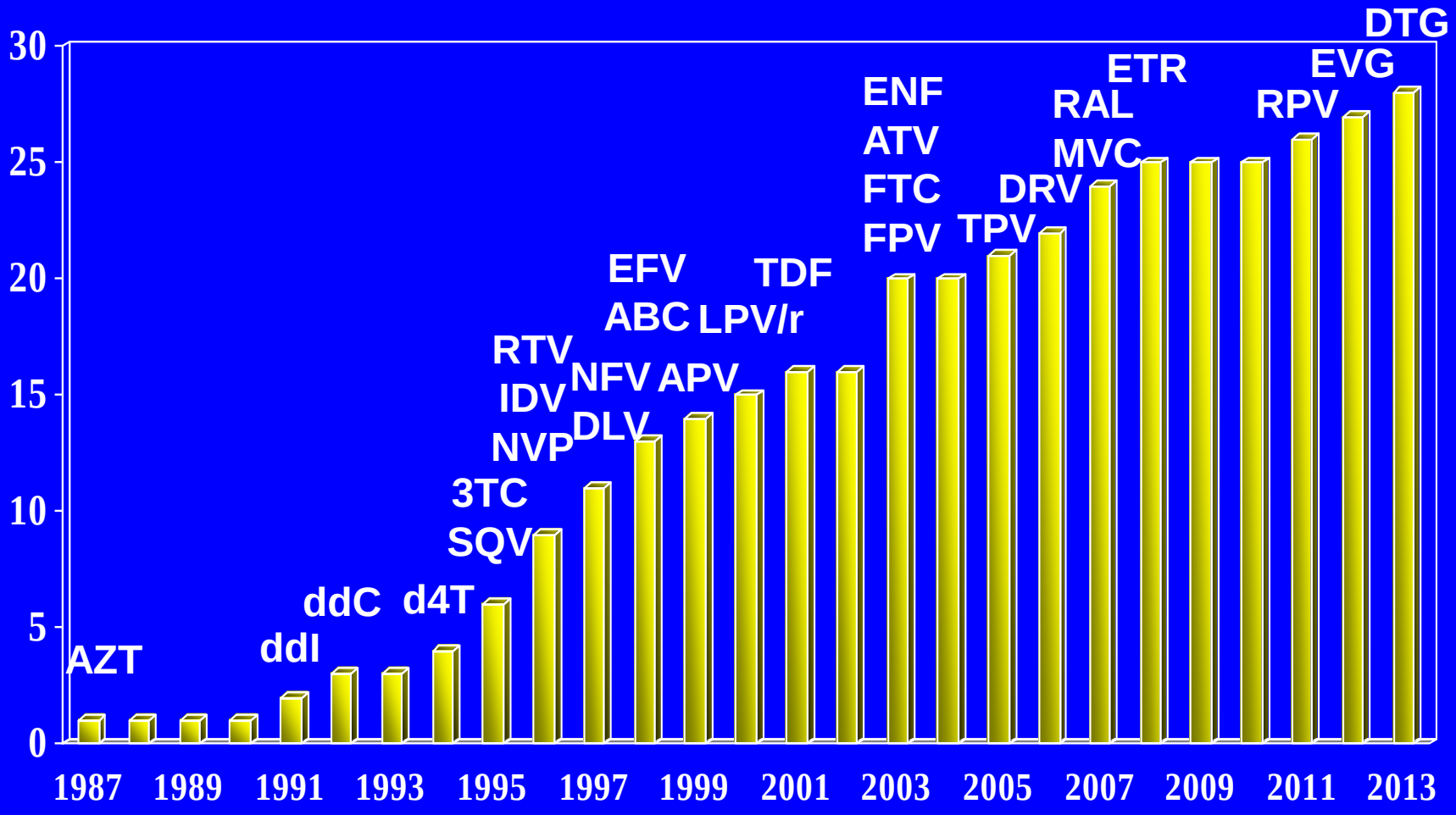
Disclosures

- I have received honoraria from AbbVie, Gilead, Merck, ViiV

Antiretroviral Drug Approval: 1987 - 2014



Antiretroviral Drugs: 2014

nucleoside/tide RTIs (NRTIs)

- zidovudine (ZDV, AZT)
- didanosine (ddI)
- stavudine (d4T)
- lamivudine (3TC)
- abacavir (ABC)
- emtricitabine (FTC)
- tenofovir (TDF)

NNRTIs

- nevirapine (NVP)
- delavirdine (DLV)
- efavirenz (EFV)
- etravirine (ETR)
- rilpivirine (RPV)

protease inhibitors (PIs)

- saquinavir (SQV)
- ritonavir (RTV)
- indinavir (IDV)
- nelfinavir (NFV)
- lopinavir/r (LPV/r)
- atazanavir (ATV)
- fosamprenavir (FPV)
- tipranavir (TPV)
- darunavir (DRV)

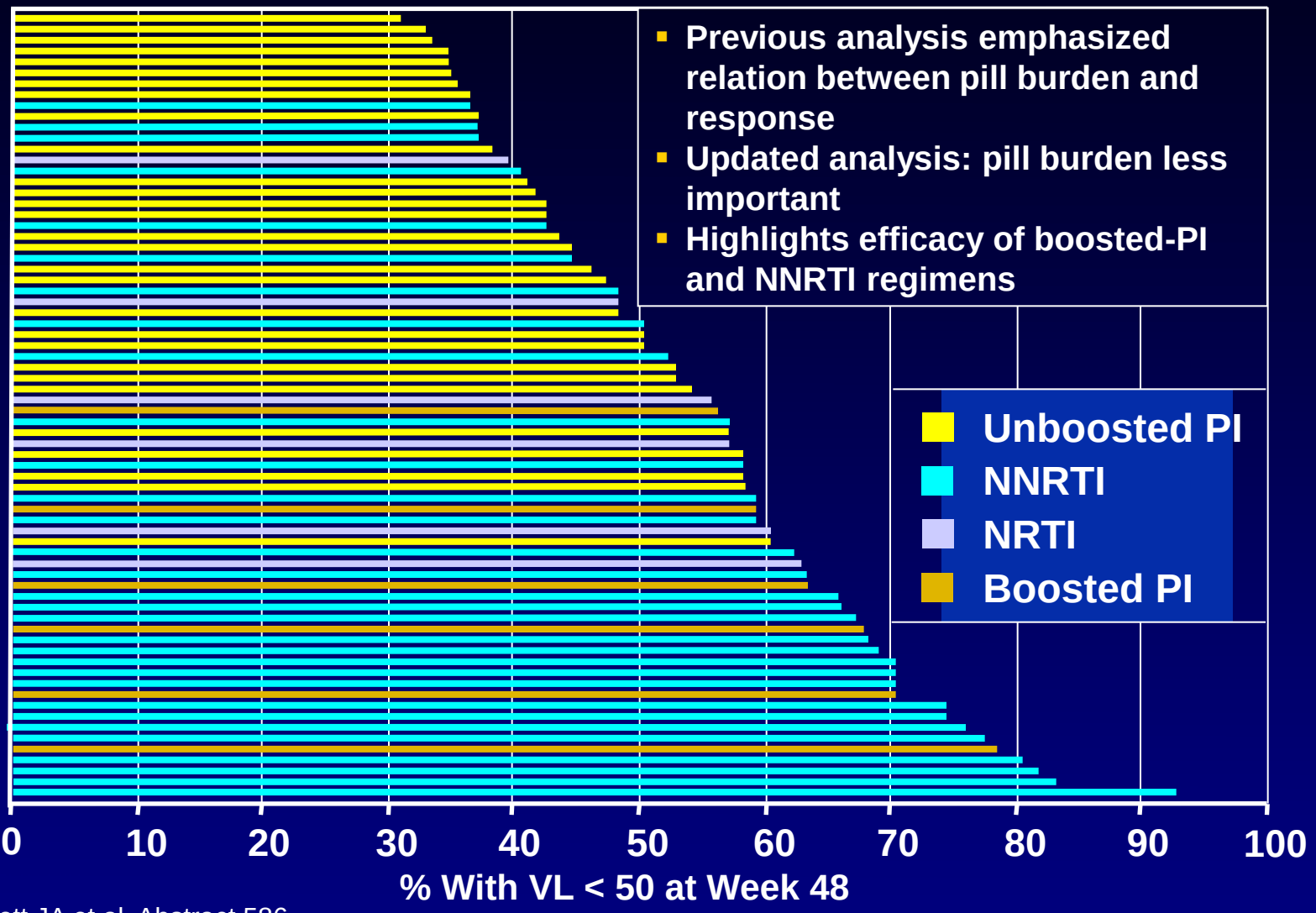
entry inhibitors (EIs)

- enfuvirtide (T-20, fusion inhibitor)
- maraviroc (MVC, CCR5 antagonist)

integrase inhibitors (IIs)

- raltegravir (RAL)
- elvitegravir (EVG)
- dolutegravir (DTG)

Collated Results of HAART Studies



Bartlett JA et al. Abstract 586.

Major Progress

HIV disease has been transformed for most people into a chronic manageable condition.

The drugs really work!!

Cohen C, et al. 6th IAS 2011; Abstract TULBPE032

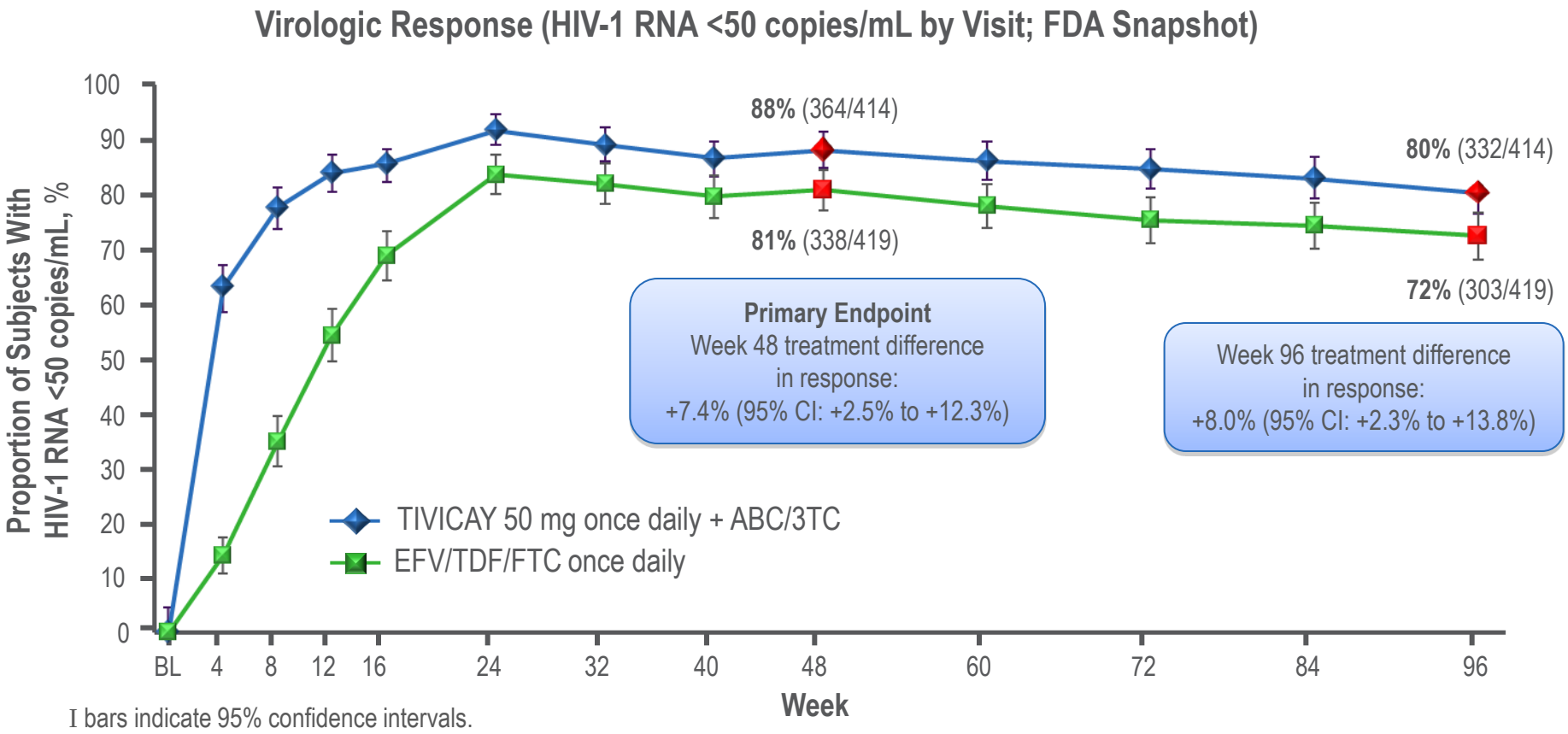
But problems still exist:

1. Viral transmission
2. Drug resistance
3. Transmission of drug resistance
4. Drug toxicities
5. Long-term consequences of HIV itself and/or ARVs

Cohen C, et al. 6th IAS 2011; Abstract TULBPE032

And, most importantly, the use of sub-optimal therapeutic regimens in developing country settings risks exacerbating the problems of selected and transmitted drug resistance.

Efficacy Results



I bars indicate 95% confidence intervals.

- The difference in virologic efficacy results with TIVICAY + ABC/3TC versus EFV/TDF/FTC was driven primarily by the rates of discontinuation due to AEs (3% vs 11%, respectively, at Week 96)

AE, adverse event; CI, confidence interval.

Walmsley SL et al. *N Engl J Med.* 2013;369(19):1807-1818.
Data on file, ViiV Healthcare.

Summary of Adverse Events

AEs, n (%)	TIVICAY 50 mg once daily + ABC/3TC (n=414)	EFV/TDF/FTC once daily (n=419)
AEs leading to discontinuation	14 (3)	52 (12)
Serious drug-related AEs	1 (<1)*	9 (2)†
Fatal AEs	0	2 (<1)‡

*1 drug hypersensitivity.
†4 psychiatric, 2 syncope, 1 cerebral vascular accident, 1 hypersensitivity, 1 renal failure.
‡n=1, renal and respiratory failure; n=1, pneumonia.

Data on file, ViiV Healthcare.

Treatment-Emergent Resistance

- Patients included in the resistance analysis subset (n=8) had HIV-1 RNA >400 copies/mL at failure or last visit through Week 96 and had resistance data

	TIVICAY 50 mg once daily + ABC/3TC
Patients with INSTI mutations with decreased susceptibility to TIVICAY	0
Patients with NRTI mutations with decreased susceptibility to NRTIs	0
Patients with INSTI resistance substitution without decreased susceptibility to TIVICAY	1* (E157Q/P)

*This patient had 275 copies/mL HIV-1 RNA at Week 24.
NRTI, nucleoside reverse transcriptase inhibitor = ABC, 3TC.

- No patients had detectable decreases in susceptibility to TIVICAY or ABC/3TC in the resistance analysis subset

Manulife to offer life insurance to HIV-positive Canadians for 1st time

As life expectancy for HIV-positive people rises, it is seen as chronic illness that is manageable

By Pete Evans, CBC News Posted: Apr 22, 2016, 12:48 PM ET

A small clinical study termed PADDLE suggests that DTG/3TC may be equivalent to DTG/3TC/ABC and also failed to document resistance over 24 weeks.

Resistance to INSTIs in clinical trials in treatment-naïve patients

Treatment	Major resistance mutations detected by genotyping in treatment-naïve patients failing therapy	Minor resistance mutations
Raltegravir	Y143 N155H Q148	Multiple
Elvitegravir	T66I E92Q N155H Q148	Multiple
Dolutegravir	NONE	NONE

RALTEGRAVIR
Cooper et al., NEJM, 2008
Sichtig et al, JAC, 2009
Canducci et al, AIDS, 2009
Hatano et al, JAIDS, 2010

ELVITEGRAVIR
Sax et al, Lancet, 2012
DeJesus et al, Lancet, 2012

DOLUTEGRAVIR
vanLunzen et al., Lancet Infect. Dis., 2012

Major resistance pathways against INSTIs (clinical and tissue culture data)

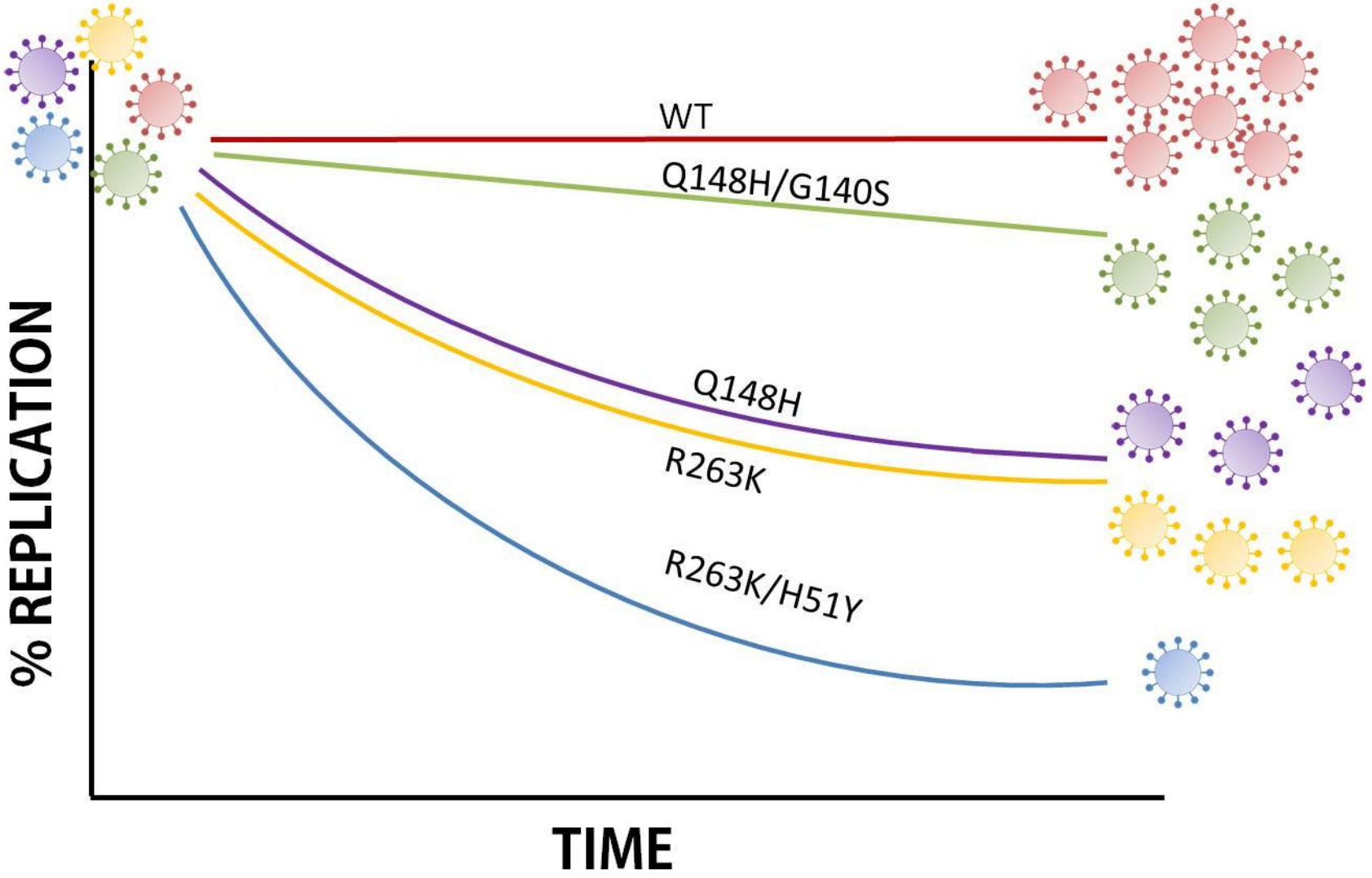
Mutational pathways	Fold resistance		
	RAL	EVG	DTG
Y143 pathway			
Y143C	<10	<2	<2
Y143R	<50	<2	<2
T97A/Y143C	>100	<2	<2
T97A/Y143R	>100	<2	<2
L74M/T97A/Y143G	<50	ND	<2
L74M/T97A/E138A/Y143C	<20	ND	<2
N155 pathway			
N155H	**<50**	**<50**	**<2**
E92Q/N155H	**<100**	**>100**	**<10**
L74M/N155H	**<50**	**<50**	**<2**
Q148 pathway			
Q148H	<20	<10	<2
Q148K	<100	<100	<2
Q148R	<50	<100	<2
E138K/Q148H	<10	<20	<2
E138K/Q148K	>100	>100	<20
E138K/Q148R	>100	>100	<10
G140S/Q148H	>100	>100	<20
G140S/Q148K	<10	<100	<2
G140S/Q148R	>100	>100	<10
E138A/G140S/Y143H/Q148H	>100	ND	<50
R263K pathway			
R263K	<1	3	4
R263K/H51Y	3-5	3	4-6

Quashie et al., Curr. Opin. Infect. Diseases, in press

R263K pathway	RAL (fold-resistance)	EVG (fold-resistance)	DTG (fold-resistance)
R263K	<1	3	4
R263K/H51Y	3-5	3	4-6

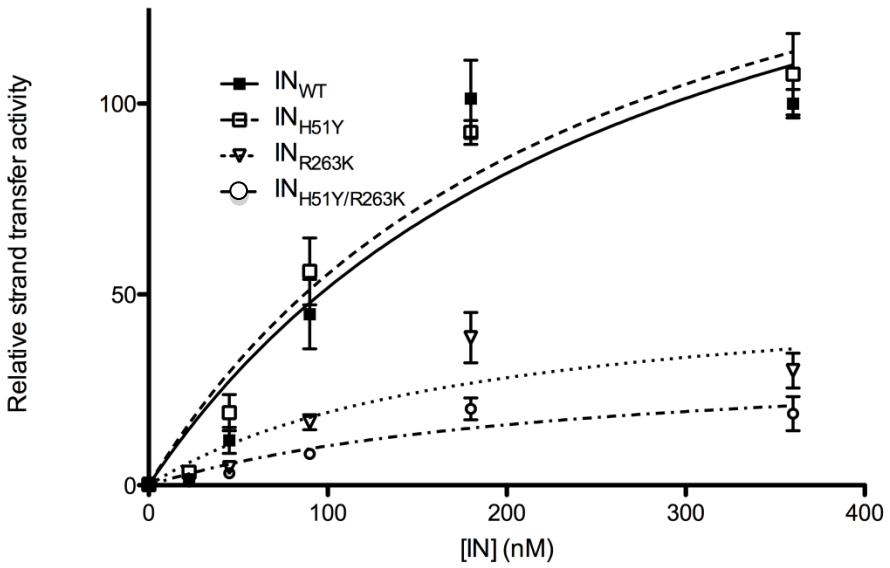
Quashie et al., Curr. Opin. Infect. Diseases, in press

Viruses that contain the R263K (and H51Y) mutation(s) after selection by DTG are so impacted in regard to fitness that they are never observed in patients.


WT
Q148H/G140S
Q148H
R263K
R263K/H51Y
% REPLICATION
TIME

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

A



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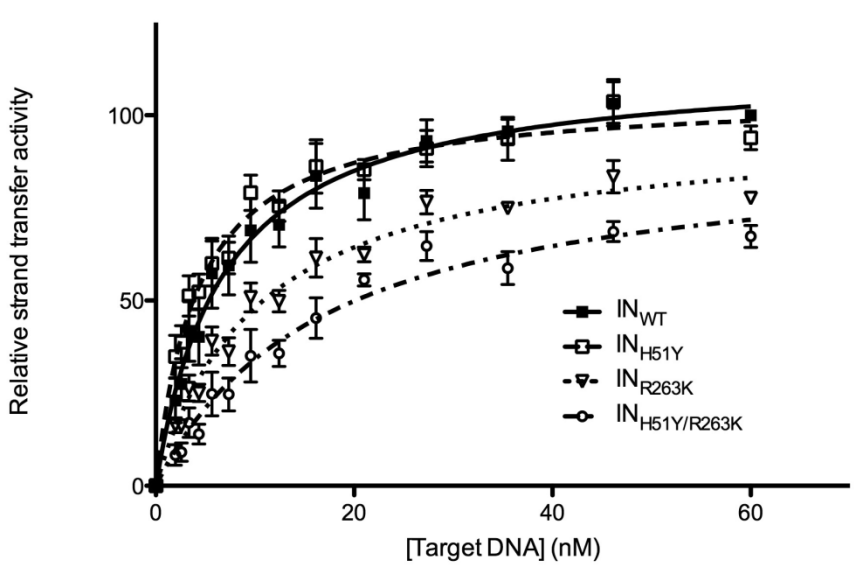
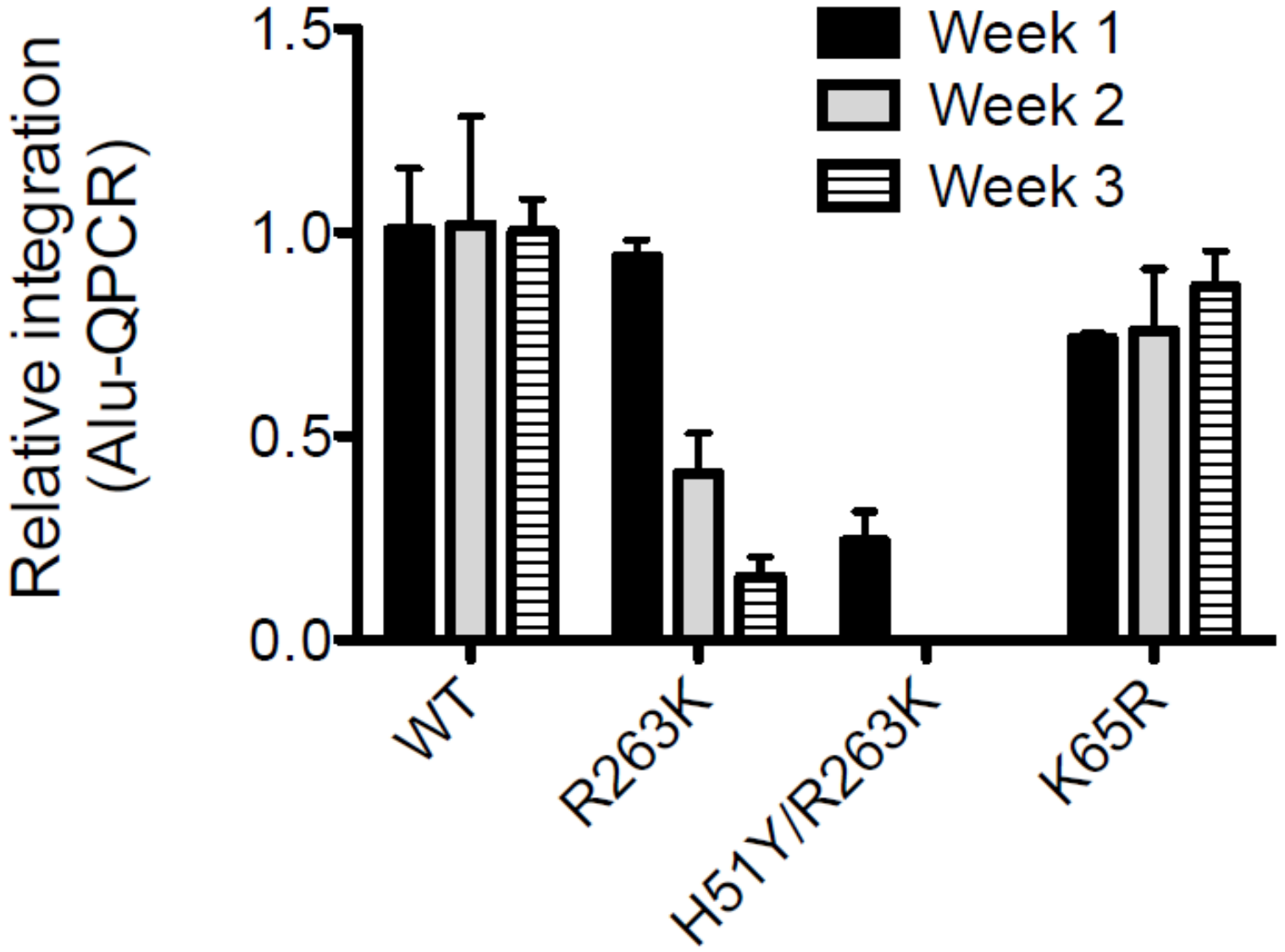


Replication Capacity of HIV Containing Various Combinations of INSTI Resistance Mutations

Mutation(s)	% fitness
E92Q	≈ 75%
Y143	≈ 72%
Q148	≈ 75%
N155	≈ 75%
R263K	≈ 70%
G140/Q148	≈ 95%
R263K/H51Y	≈ 25%
R263K/E138K	≈ 25%
R263K/Q148R	<5%
R263K/Y143C	<5%


Relative integration
(Alu-QPCR)
1.5
1.0
0.5
0.0
Week 1
Week 2
Week 3
WT
R263K
H51Y/R263K
K65R

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