Is HIV Drug Resistance Still Important in the Aftermath of Widespread Therapeutic Success?

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

Disclosures

- I have received honoraria from
- Abbott, Bristol Myers Squib, Gilead, Janssen,Merck, ViiV

Sexual Transmission of Drug Resistance Mutations

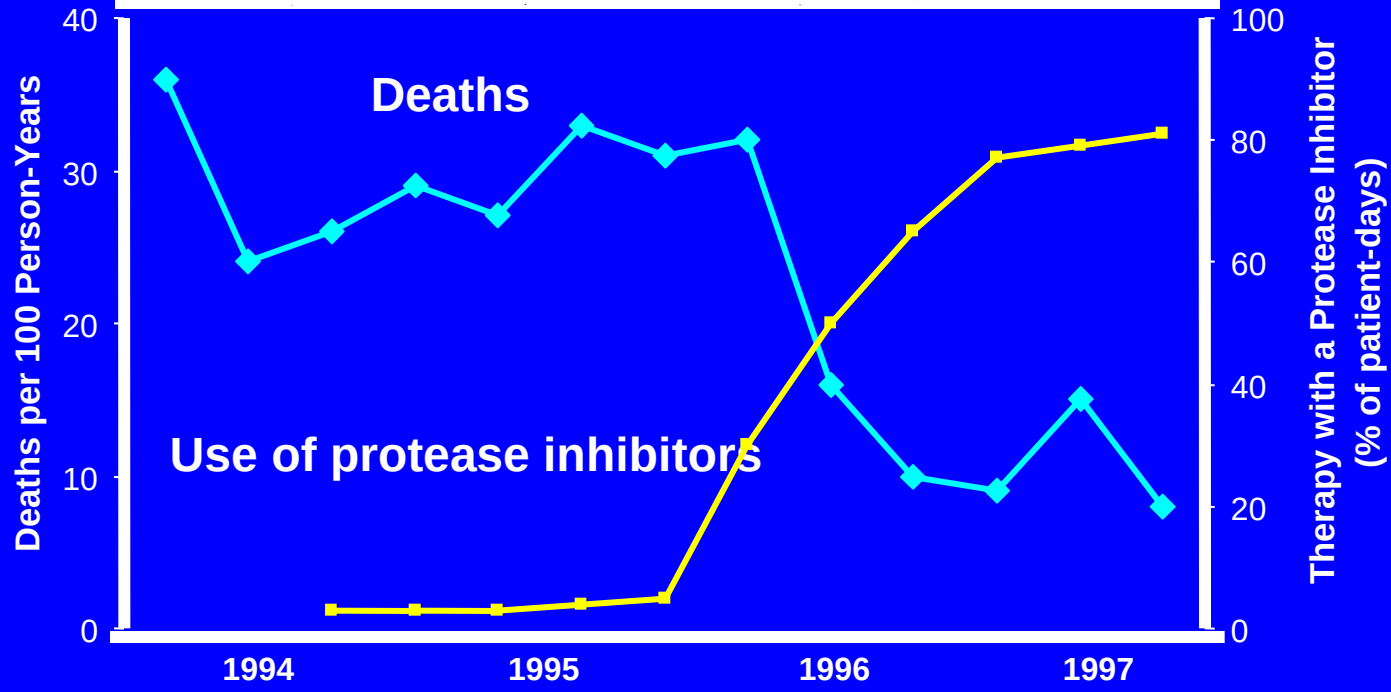
- Approximately 5-10% of all new HIV infections in developed countries now include at least one drug-resistance related mutation.
- Transmitted drug resistance is now increasingly being reported in developing countries.
- No information is yet available on whether K65R may be sexually transmitted.

The New England
Journal of Medicine

VOLUME 338 MARCH 26, 1998 NUMBER 13

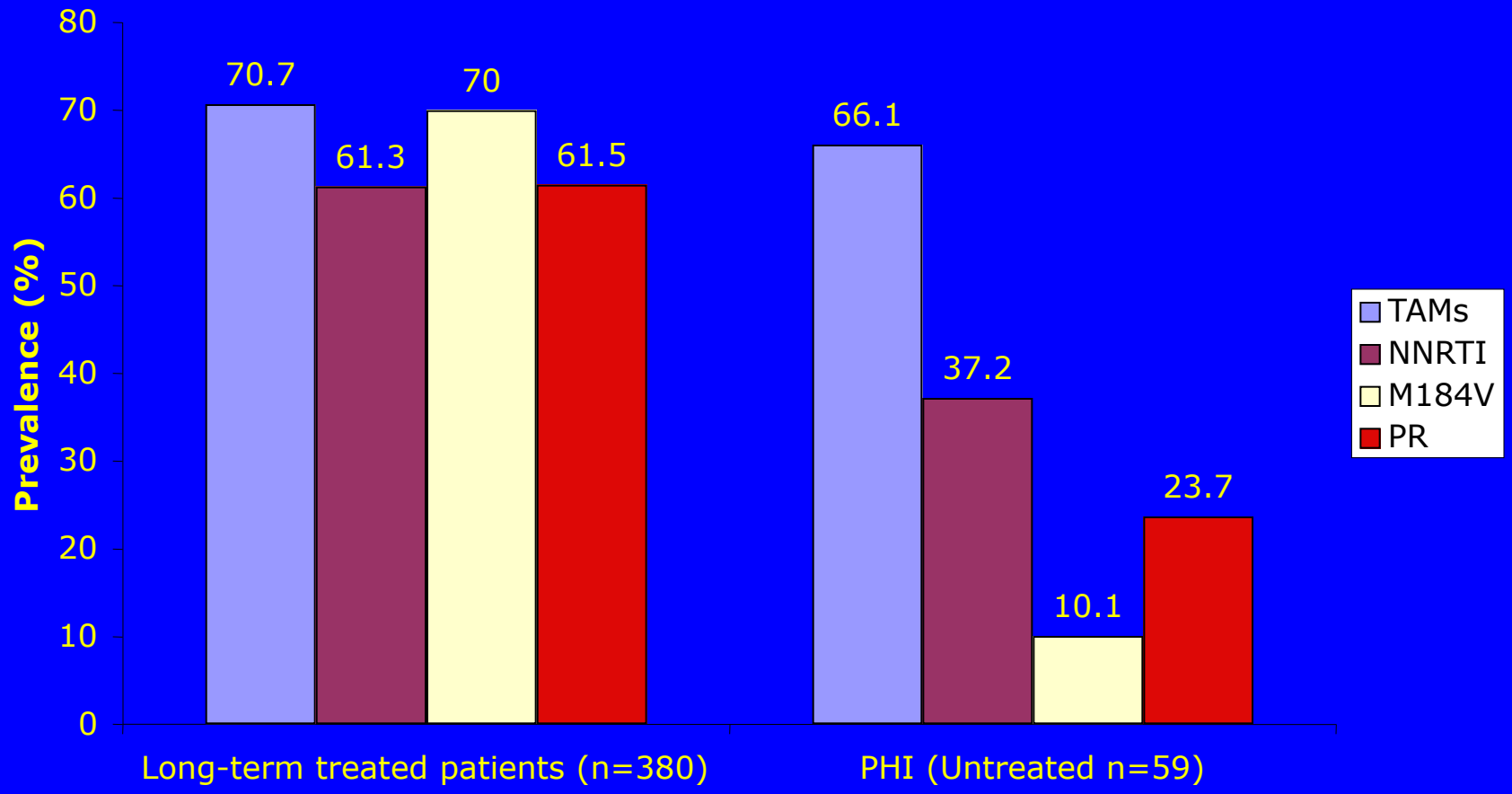
DECLINING MORBIDITY AND MORTALITY AMONG PATIENTS WITH ADVANCED HUMAN IMMUNODEFICIENCY VIRUS INFECTION

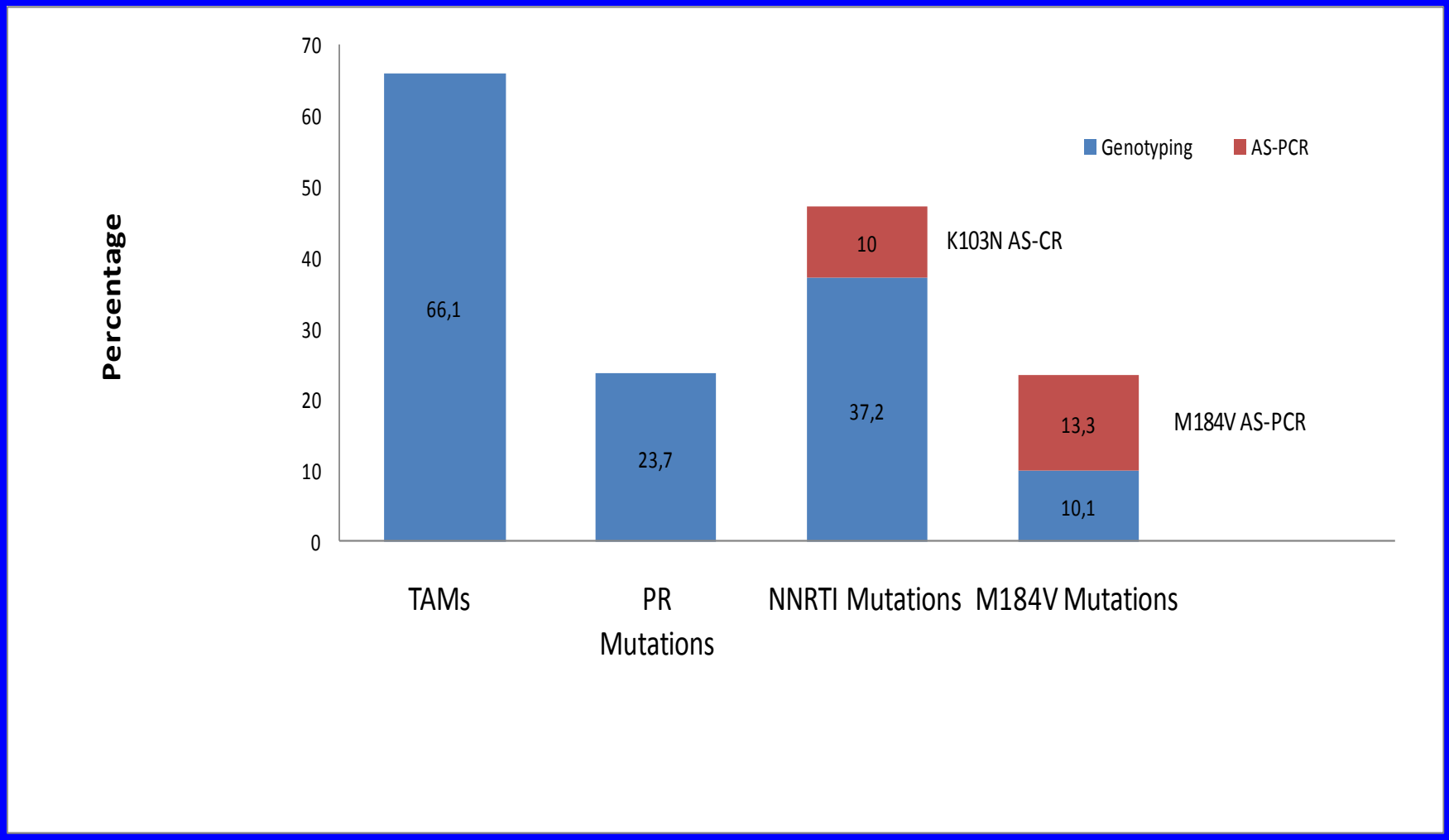
FRANK J. PALELLA, JR., M.D., KATHLEEN M. DELANEY, M.S., ANNE C. MOORMAN, B.S.N., M.P.H., MARK O. LOVELESS, M.D., JACK FUHRER, M.D., GLEN A. SATTEN, PH.D., DIANE J. ASCHMAN, R.PH., M.S., SCOTT D. HOLMBERG, M.D., M.P.H., AND THE HIV OUTPATIENT STUDY INVESTIGATORS*



Palella F, et al. *NEJM,* 1998.

Differential Presence of Select Drug Resistance Mutations in Patient Populations





% of drug-resistant mutations by genotyping and AS-PCR in acutely infected patients

Exemples de transmission de virus multirésistants dans les cas d'une primo-infection par le VIH-1

Patient	Substitutions de codon associées à une pharmacorésistance		
	Mutations - INTI	Mutations - INNTI	Mutations - IP
1	41L; 67N; 69N; 70R; 74V; 184V; 215F; 219Q	100I; 103N	10I; 36I; 54V; 63P; 71V; 73S; 82V; 90M
2	41L; 184V; 215Y	103N, 179E	48V; 63P; 71V; 73S; 77I; 82A; 90M
3	Aucune	103N	10I; 54V; 63P; 71V; 82T; 84V; 90M
4	184V; 215Y	103N	77I
5	184V	108I	20R, 77I
6	41L; 67N; 210W; 215Y	Aucune	63P; 71V; 73S; 90M
7	41L; 215Y	101E	Aucune
8	41L; 215Y	101E	Aucune

INTI : Inhibiteurs nucléosidiques de la transcriptase inverse
INNTI : Inhibiteurs non nucléosidiques de la transcriptase inverse
IP : Inhibiteurs de la protéase

Brenner, B. et coll., *AIDS, 18(12)*, le 20 août 2004, p. 1653–1660.

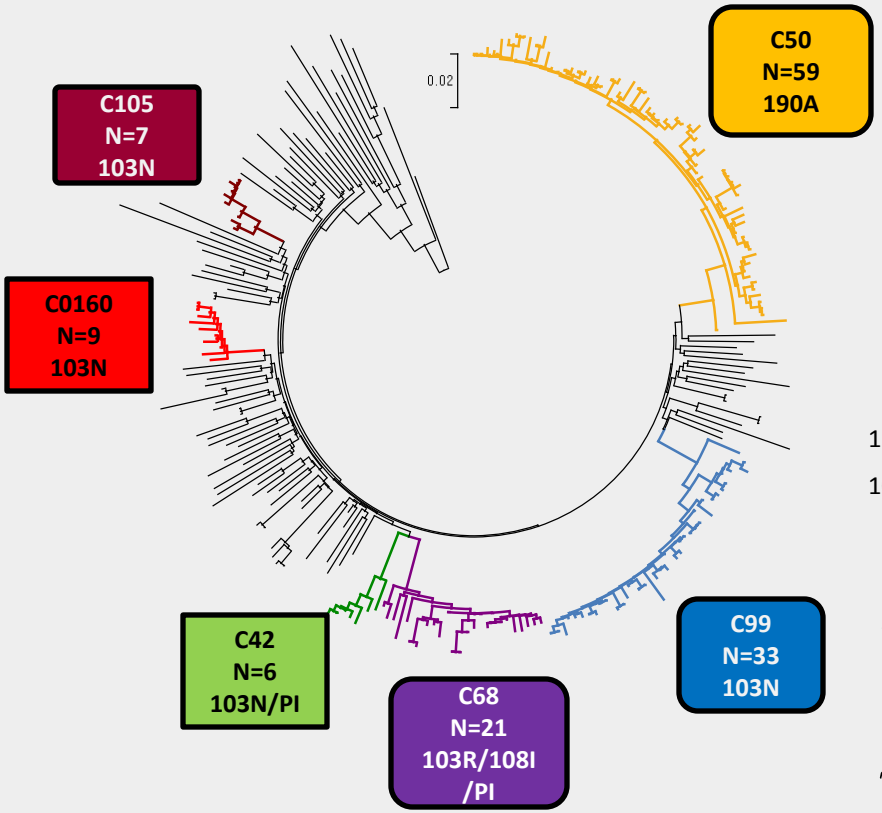
Is M184V Found Alone or Linked in Cases of Transmitted Resistance as Determined by Bulk Sequencing?

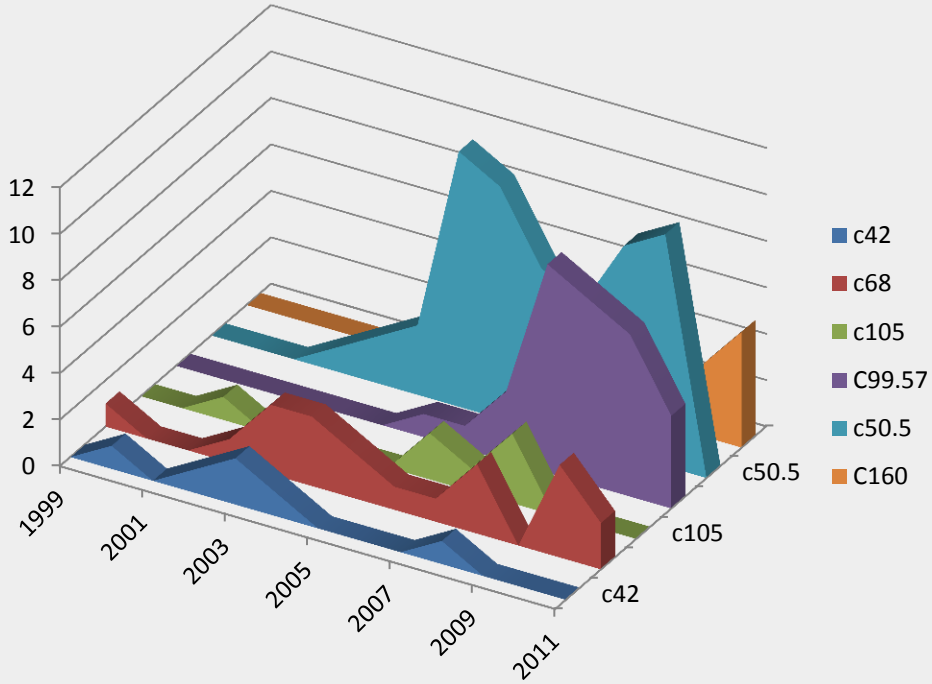
	Alone	Linked
PHI patients	2/753	15/753
Naïve non-PHI patients (>8 months post-infection)	0/863	7/863

Time to Disappearance of M184V In PHI Individual Samples as Measured by AS-PCR

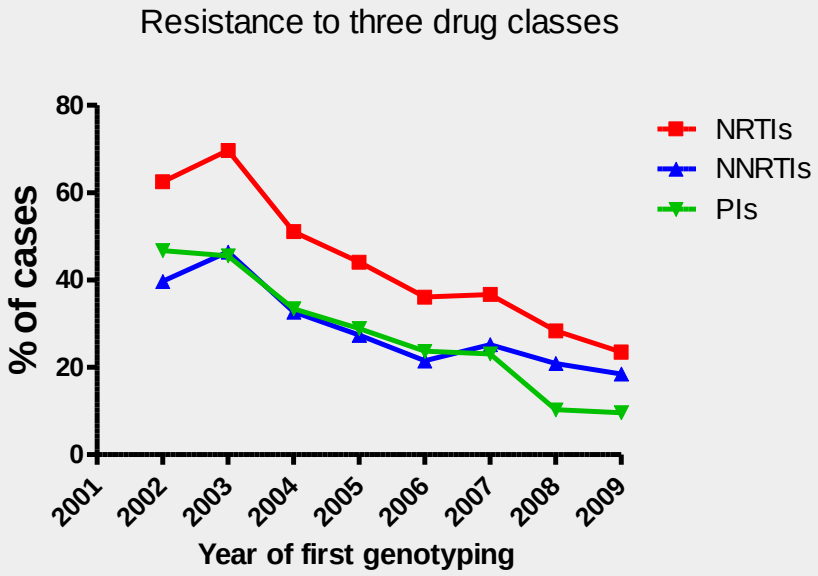
Sample	Estimated No. Weeks after Infection	% M184V
1	15	16
	30	4
	40	0
2	18	24
	33	2
	52	0

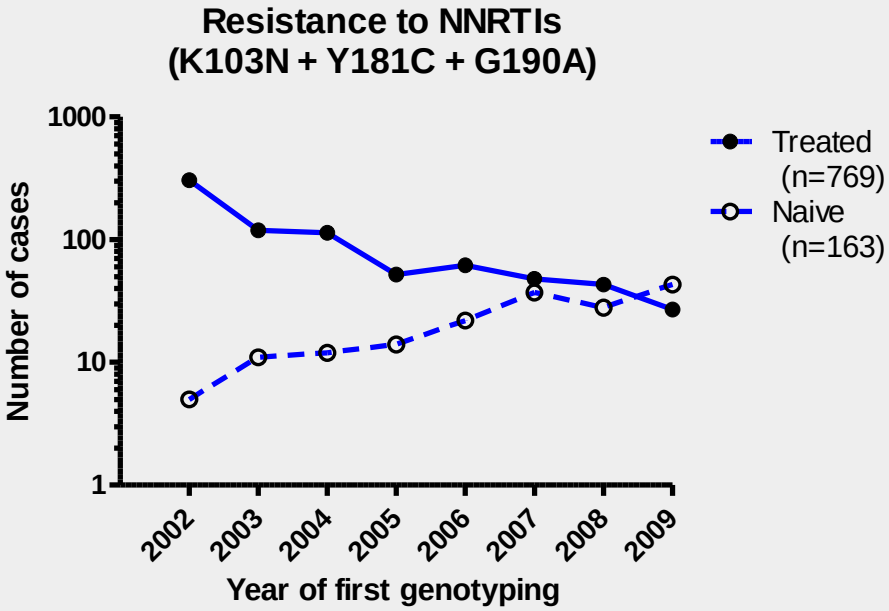
Transmitted resistance to first generation NNRTIs, e.g. efavirenz, among treatment-naïve populations n=135

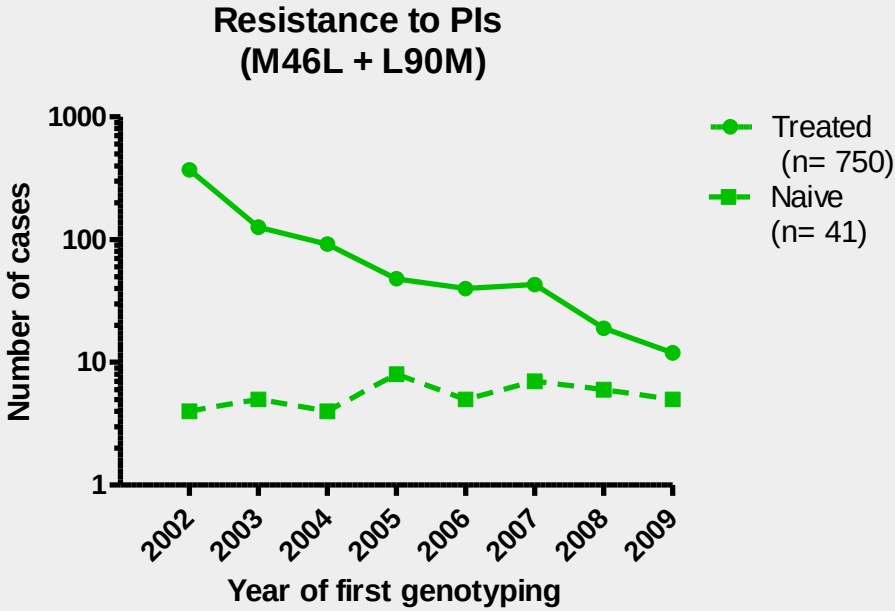




Transmitted NNRTI resistance rising in the post-HAART era



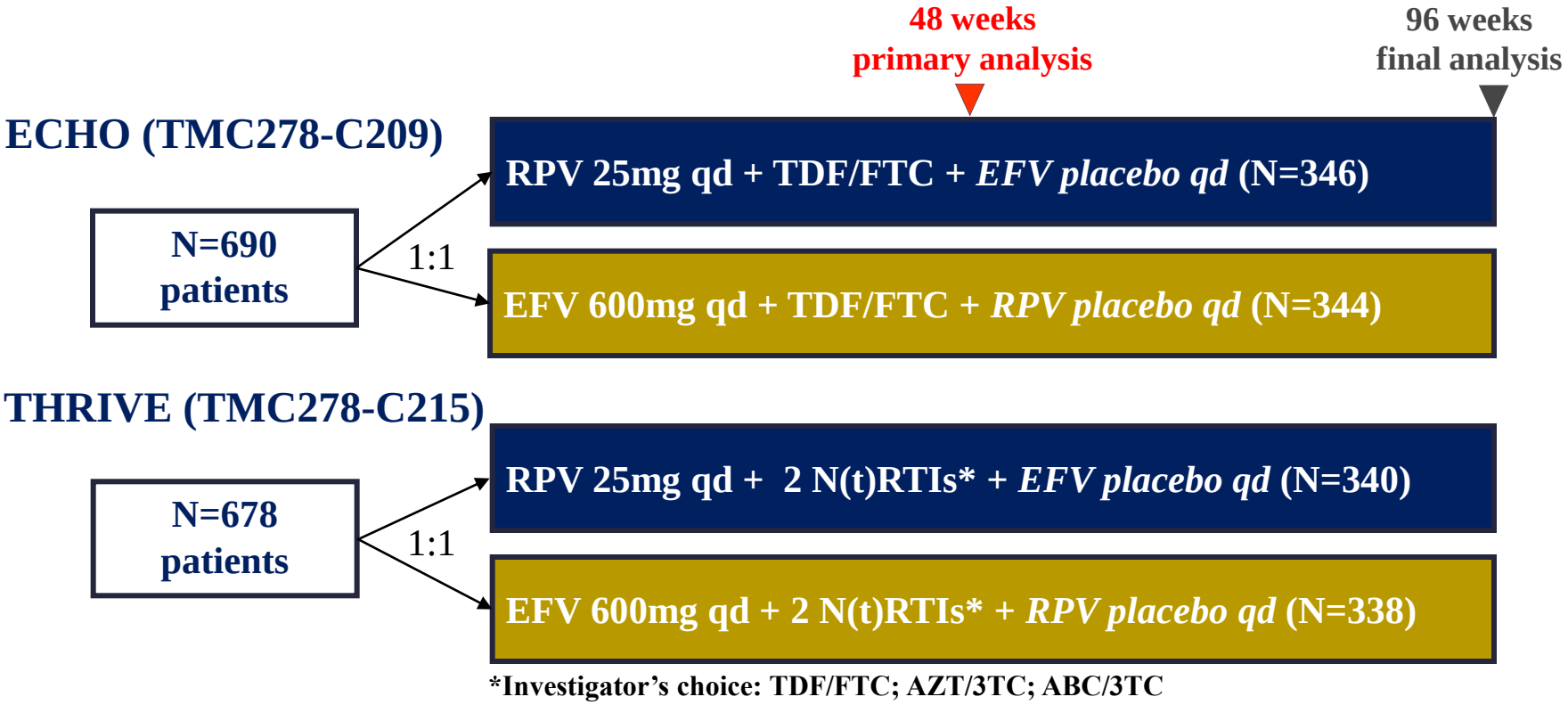




Rilpivirine: Background

- NNRTI with a long terminal half-life (34-55h) allowing QD dosing
- Approved dose is 25 mg QD, but phase 2 dose-finding studies were conducted with doses up to 150 mg QD
- Can be administered as a “free- standing” tablet formulation, or as part of a STR, in combination with emtricitabine and TDF

ECHO and THRIVE double-blind study designs



*Investigator's choice: TDF/FTC; AZT/3TC; ABC/3TC

- RPV was non-inferior to EFV in confirmed response (viral load <50 copies/mL, ITT-TLOVR) at Week 48 (primary objective)[1]
- RPV had a more favourable safety profile but higher virologic failure rate than EFV[1]
- RPV is approved in the US as a single-agent tablet[2] and a qd fixed-dose, single-tablet regimen with TDF/FTC is under development[3]

ITT = intent-to-treat; TLOVR = time-to-loss of virologic response

[1]Cohen CJ, et al. XVIIIth IAC 2010. Abstract THLBB206
[2]FDA label for EDURANT™ (rilpivirine) tablets. 2011
[3]Mathias A, et al. XVIIIth IAC 2010. Abstract LBPE17

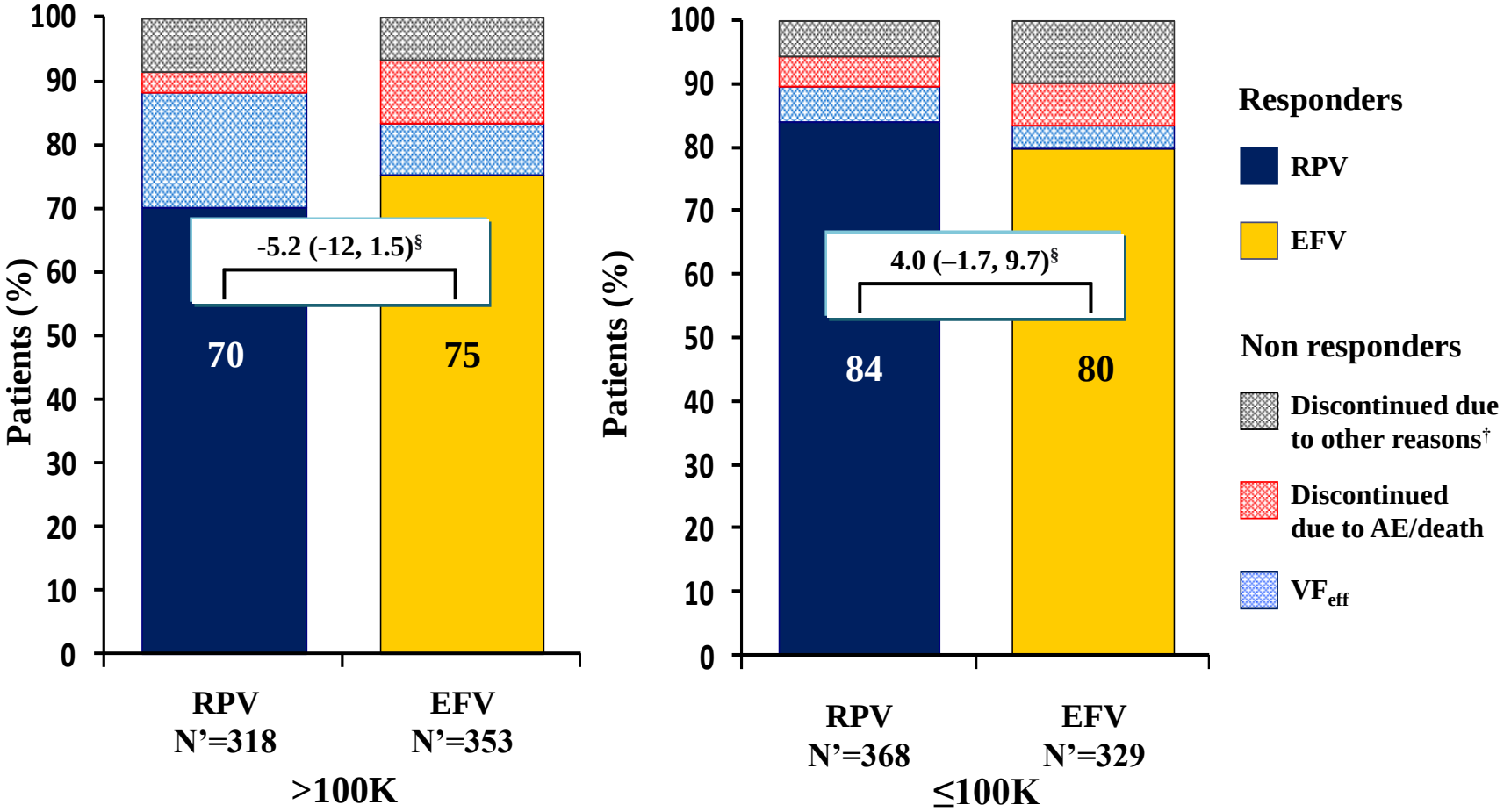
Cohen C, et al. 6th IAS 2011; Abstract TULBPE032

Pooled ECHO and THRIVE: Adverse Event Summary[a]

	Rilpivirine N=686	EFV N=682	p-value RPV vs EFV
Median treatment duration, weeks	56	56	
Any serious AE, %	7	8	NS
Any AE,%	90	92	NS
Grade 2–4 AE at least possibly related to treatment, %	16	31	<0.0001[b]
Discontinuation due to AEs, %	3	8	0.0005
Most common AEs of interest,[c] %			
Any neurological AE	17	38	<0.0001[b]
Dizziness	8	26	<0.0001[b]
Any psychiatric AE	15	23	0.0002[b]
Abnormal dreams/nightmares	8	13	0.0061[b]
Rash (any type)	3	14	<0.0001[b]

NS, non significant; [a]Safety analyses performed using all available data, including beyond Week 48; [b]Fisher's Exact test, predefined analysis for these AEs; [c]Well-described AEs associated with current NNRTIs at least possibly related to treatment and observed in ≥10% of patients in either group (all grades)

Pooled ECHO and THRIVE: ITT-TLOVR outcome at Week 96 by baseline VL



- Responses by baseline CD4 cell count were (≥200 cells/mm^3): RPV 82% vs EFV 79%, (≥50–<200 cells/mm^3): RPV 71% vs EFV 75% and (<50 cells/mm^3): RPV 56% vs EFV 69%

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

Pooled ECHO and THRIVE: summary of resistance findings

	RPV N=686			EFV N=682		
Time of failure	**All***	**Up to Week 48**	**Week 48to 96***	**All**	**Up to Week 48**	**Week 48 to 96**
VF_{res} with resistance data, n	**86**	**67**	**18**	**42**	**28**	**14**
No emergent NNRTI[1]and N(t)RTI RAMs[2], n (%)	**35 (41)**	**24 (36)**	**11 (61)**	**19 (45)**	**11 (39)**	**8 (57)**
Any emergent NNRTI[1]or/and N(t)RTI RAMs[2], n (%)	**51 (59)**	**43 (64)**	**7 (39)**	**23 (55)**	**17 (61)**	**6 (43)**
Any emergent† NNRTI RAMs[2], n (%)	**46 (53)**	**39 (58)**	**6 (33)**	**20 (48)**	**16 (57)**	**4 (29)**
Most frequent NNRTI RAM, n (%)	E138K 31 (36)	E138K 27 (40)	E138K 3 (17)	K103N 14 (33)	K103N 11 (39)	K103N 3 (21)
Any emergent† N(t)RTI RAMs[1], n (%)	**48 (56)**	**41 (61)**	**6(33)**	**11 (26)**	**9 (32)**	**2 (14)**
Most frequent N(t)RTI RAM, n (%)	M184I 32 (37)	M184I 27 (40)	M184I 4 (22)	M184V 6 (14)	M184V 6 (21)	M184I 2 (14)

*One VF_{res} occurred after Week 96 in RPV group (E138K, K219E, M184I); †At least one emergent NNRTI RAM (from the NNRTI RAM list)[1] or IAS-USA N(t)RTI[2] RAM

[1]Tambuyzer L et al. Antivir Ther 2009;14:103–9
[2]Johnson VA et al. Top HIV Med 2009;17:138–45

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

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

M184I vs M184V

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

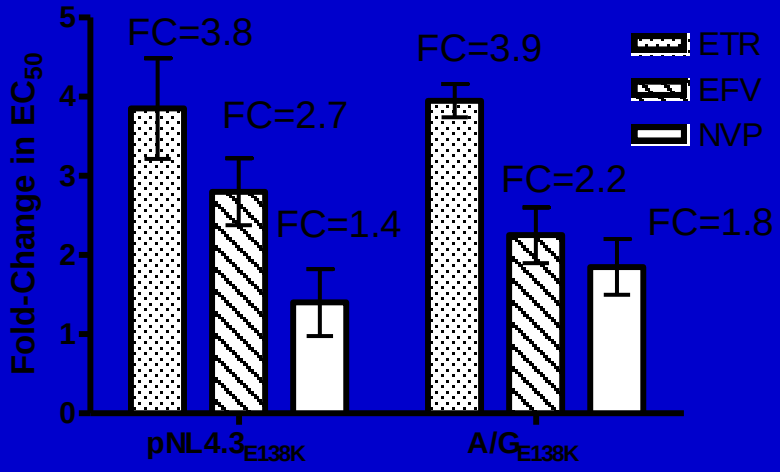
ATG ➡ ATA

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

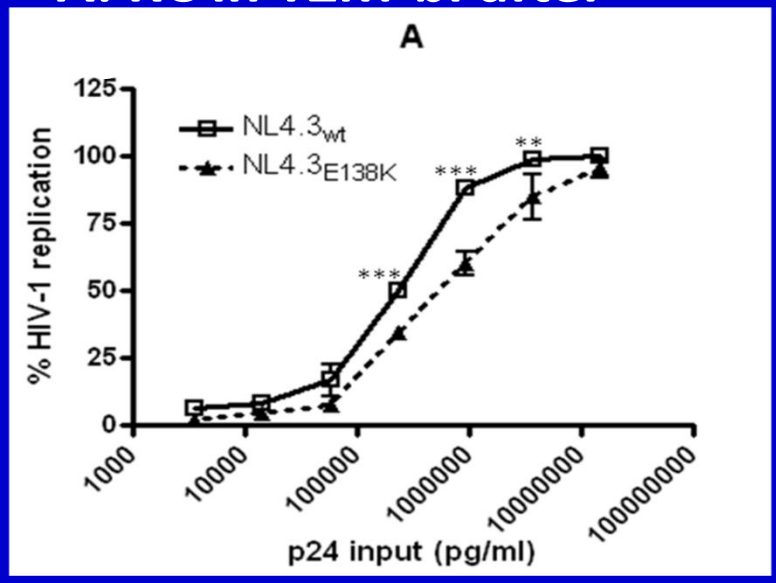
ATG ➡ GTG

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

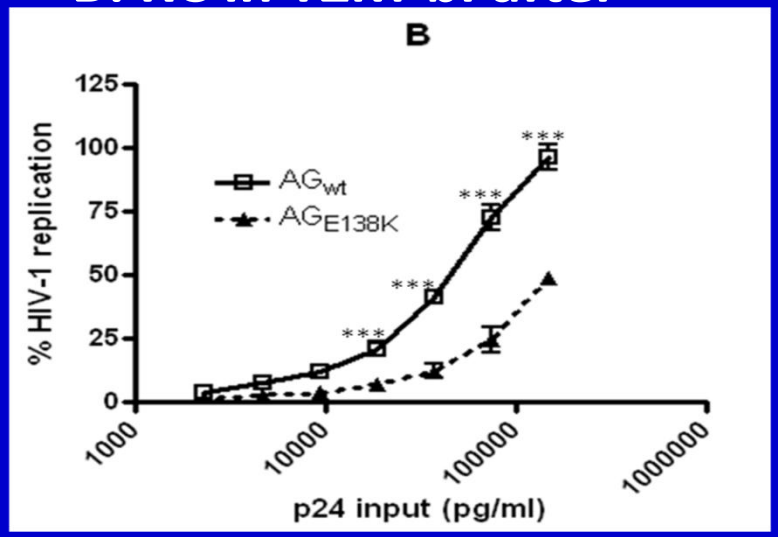
Impact of E138K in recombinant HIV-$1_{NL-4.3}$ and HIV-1_{AG} viruses on NNRTIs susceptibility and replication capacity (RC)



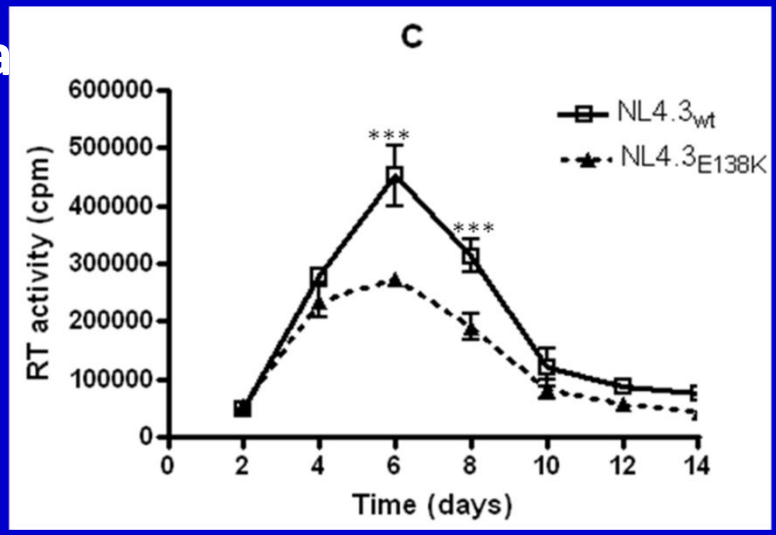
A: RC in TZM-bl after



B: RC in TZM-bl after



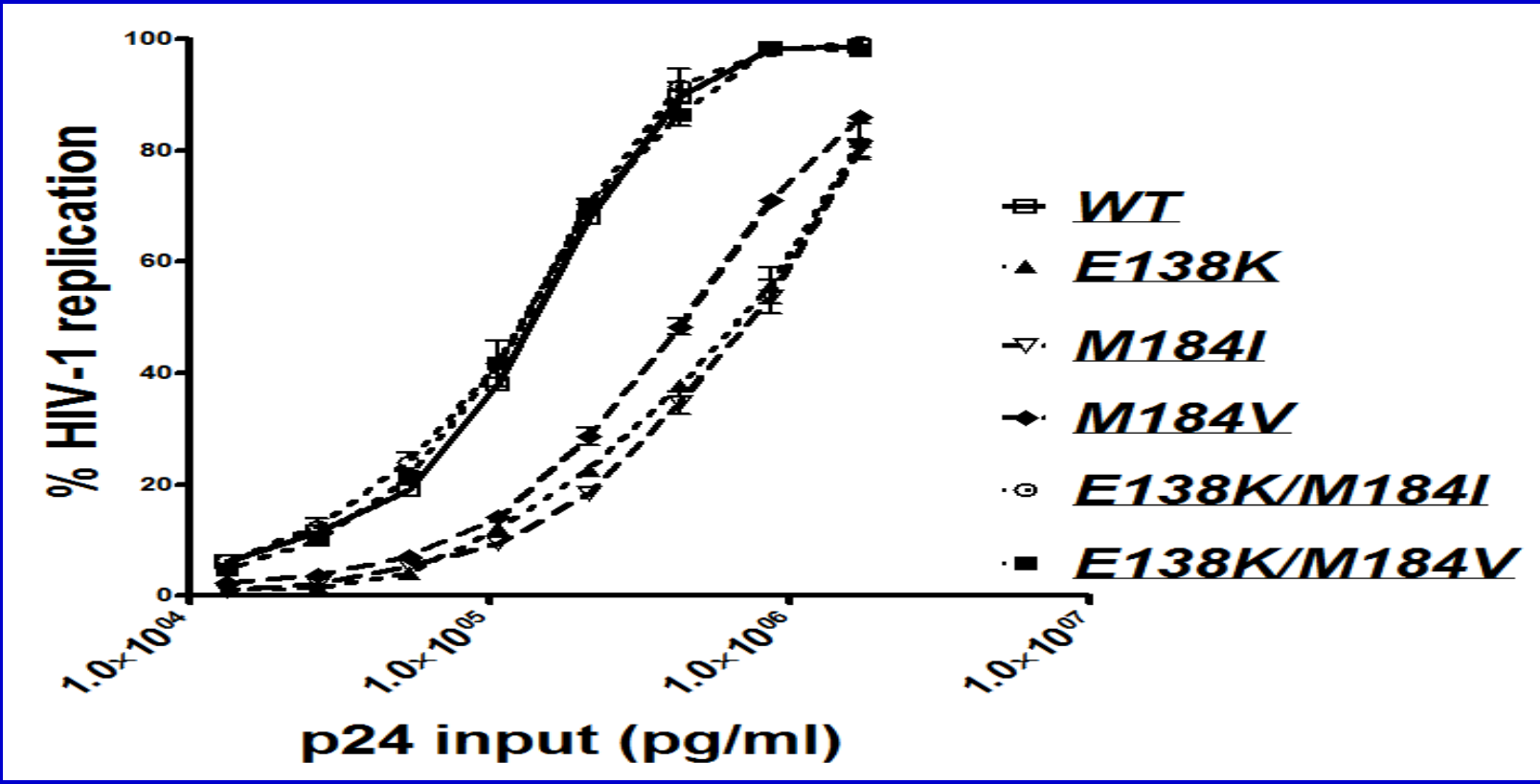
C: Growth curve in CBMCs a



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

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

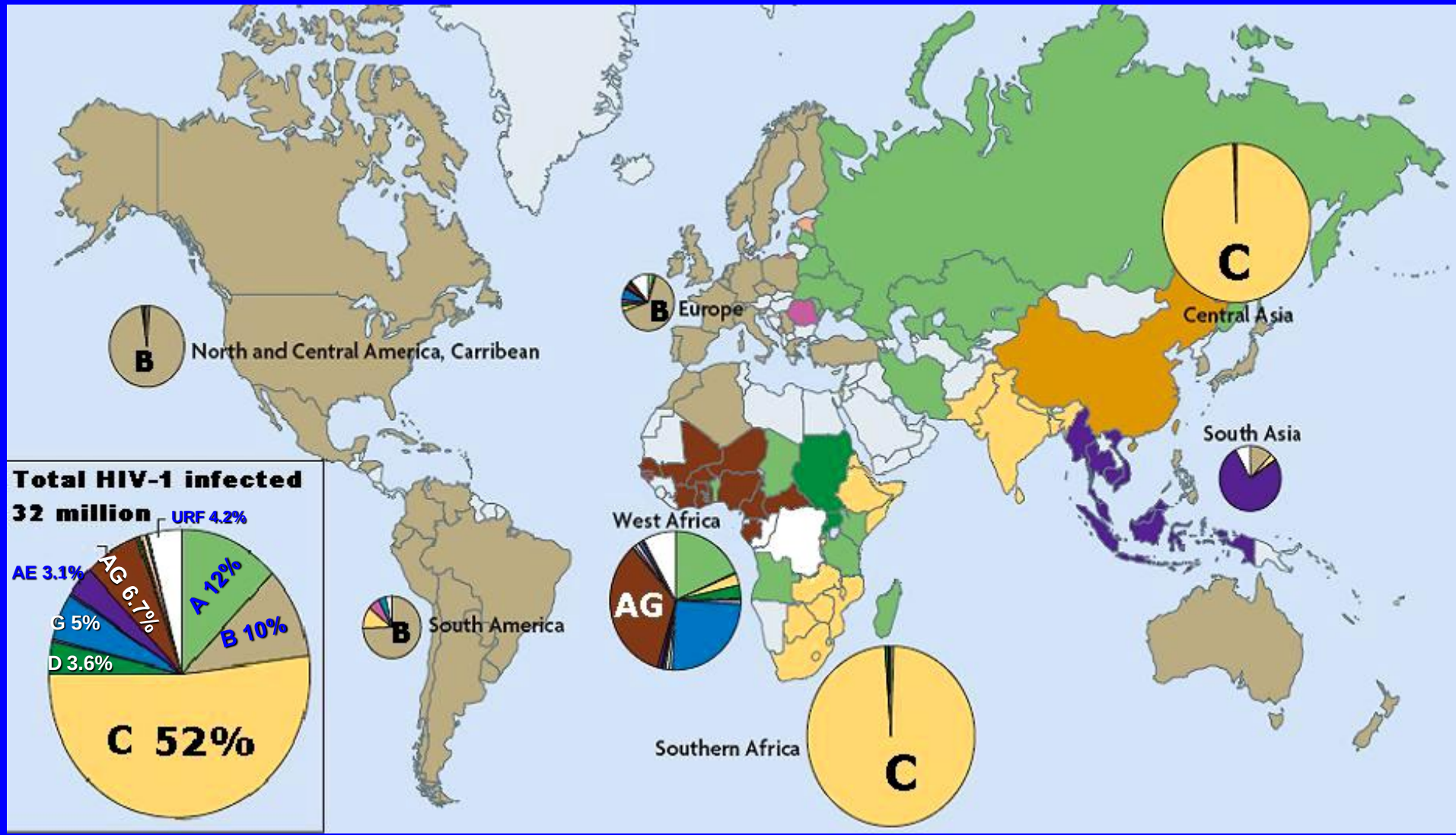
Compensatory effect of E138K on the replication capacity (RC) of M184I/V.



✓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 .

Global distribution of HIV-1 subtypes



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				

Quashie, et al, *Journal of Virology* 2012

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				

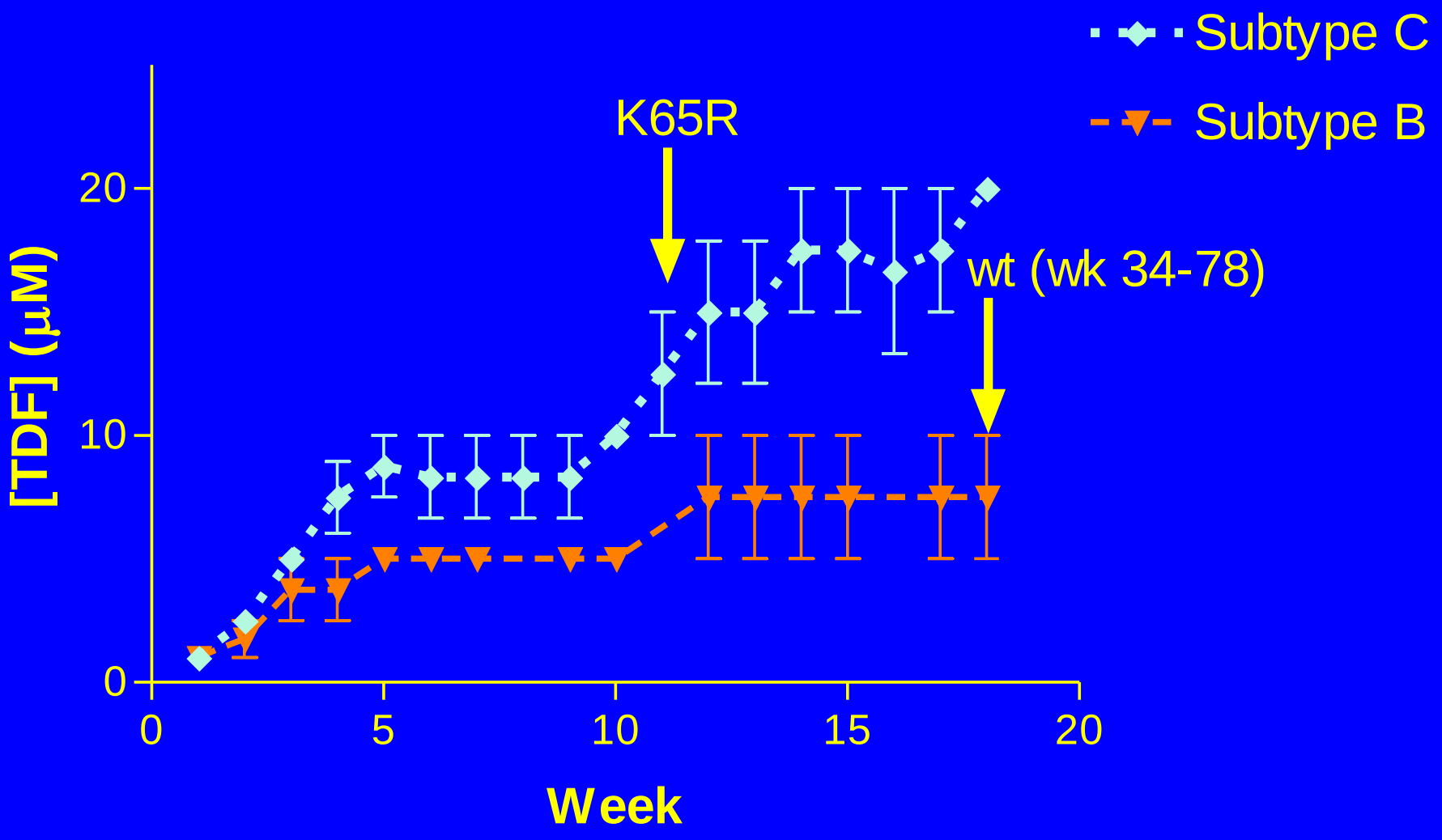
Quashie, et al, *Journal of Virology* 2012

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				

Quashie, et al, *Journal of Virology* 2012

Rapid Selection of K65R Resistance in Subtype C Isolates



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

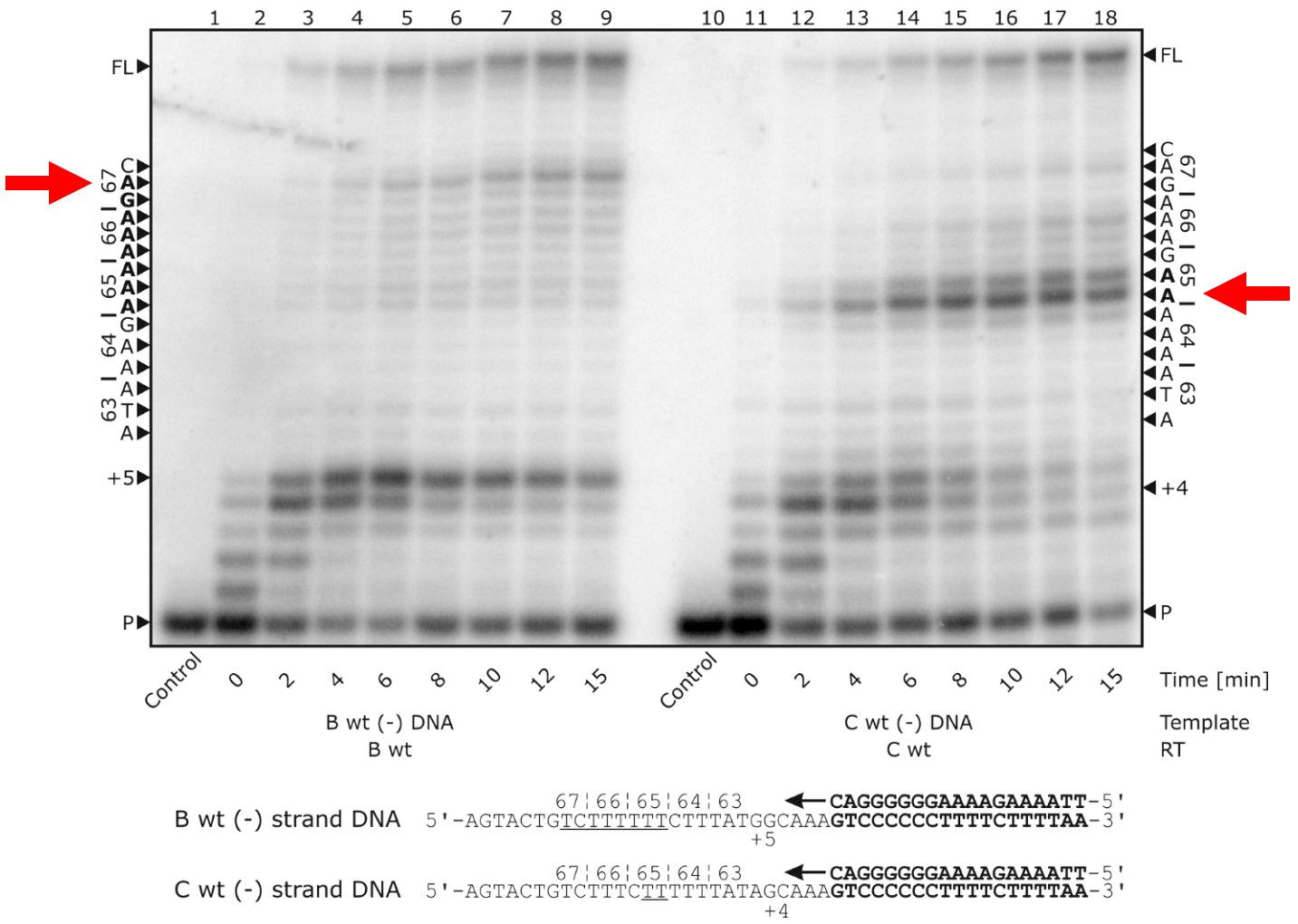
No. Patients	23
No. Patients failing	15
No. Patients with K65R	7
No. Patients with L74V	0

Background

- **The Malawi ART program scale-up:**
  - **>150,000 patients started on d4T/3TC/NVP**
- **A substantial minority with have virologic failure and eventually clinical failure.**
- **In failing patients resistance will be present**
  - **Few data from Africa on resistance patterns**

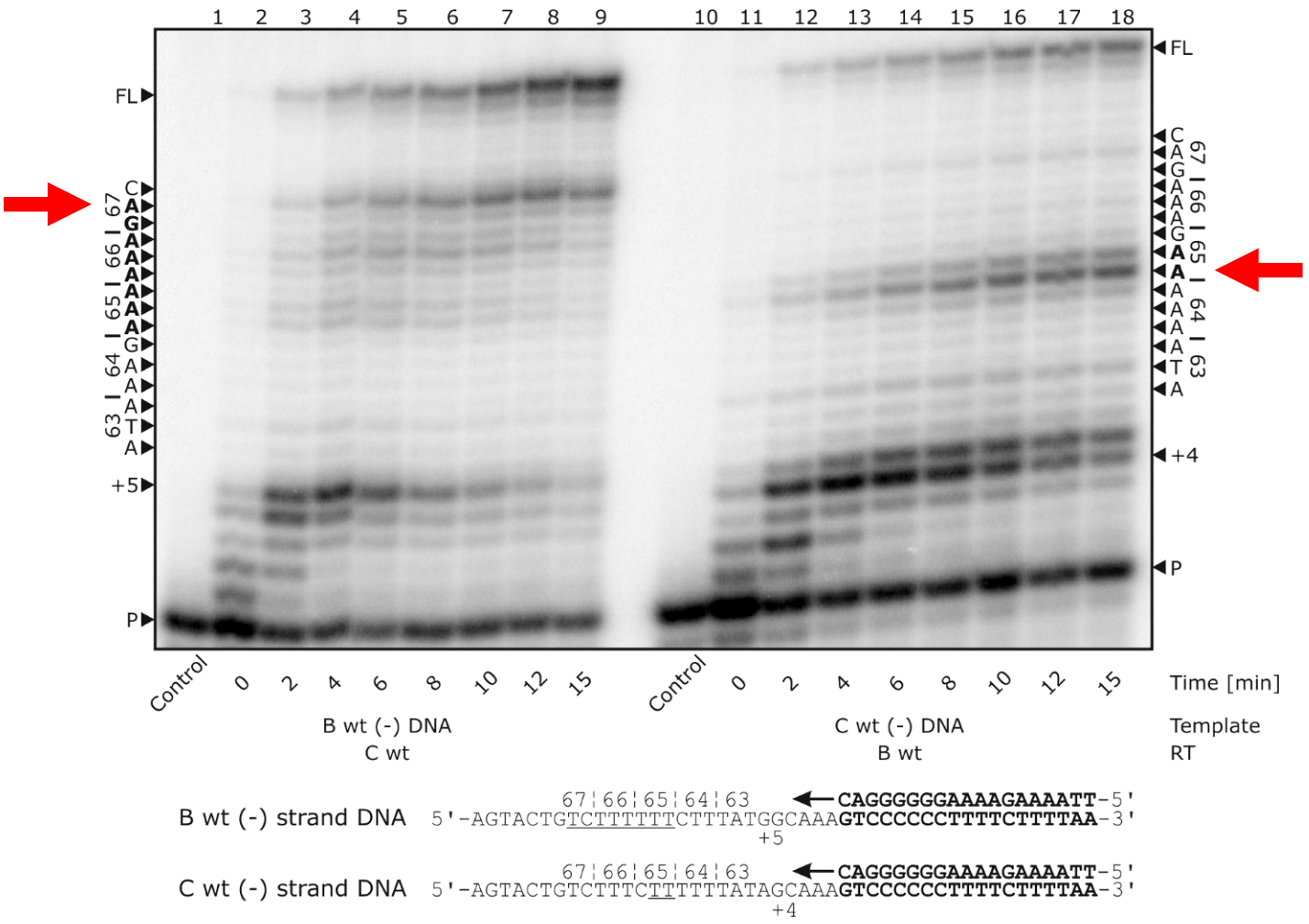
Resistance Patterns	**%**
NNRTI mutations +/-184V containing virus + additional mutations	
TAM Containing Virus	56%
Tenofovir mutations (K65R or K70E)	23%
Tenofovir & TAM	7%
Q151M Complex	19%
Pan-Nucleoside Mutation Combinations	
Q151M Complex & **Tenofovir** mutations	16%
69 insertion	1%
Pan-Nucleoside (Q151 & TDF associated mutations or 69 insertion)	17%

(+)strand DNA synthesis (1)



Only the subtype C sequence triggers a pausing site that increases the probability of a nucleotide misincorporation event which in turn leads to the K65R mutation.

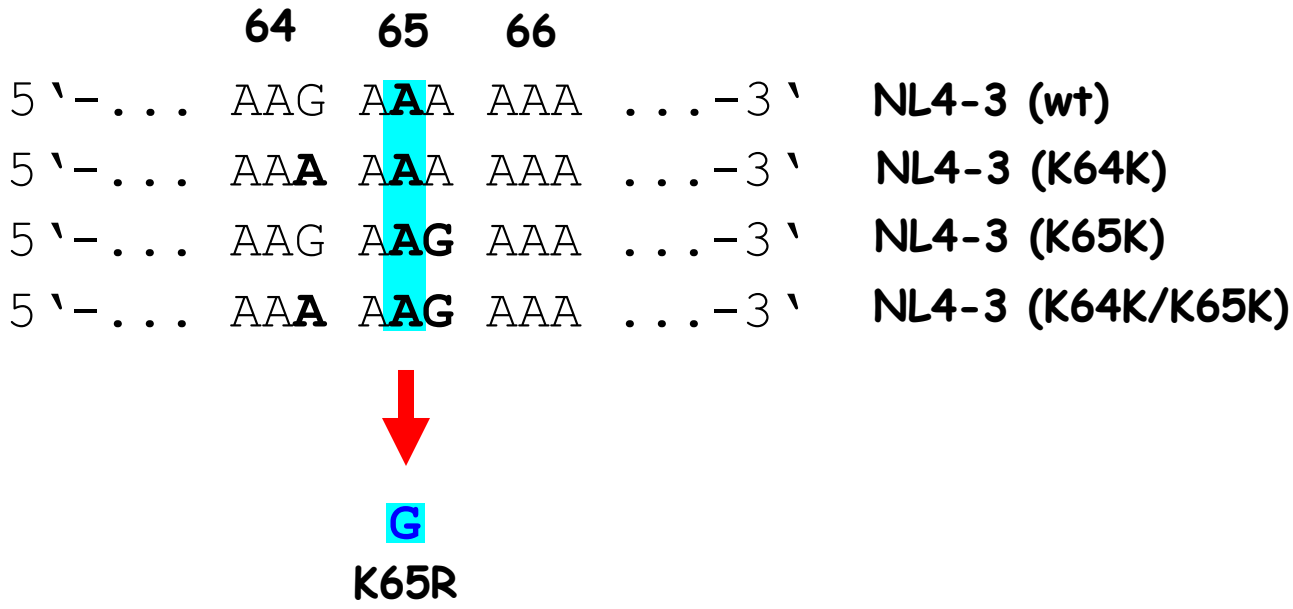
(+)strand DNA synthesis (2)



The pausing patterns are driven by the nucleotide templates and are independent of the RT enzymes used (subtype B vs C).

Validation in cell culture

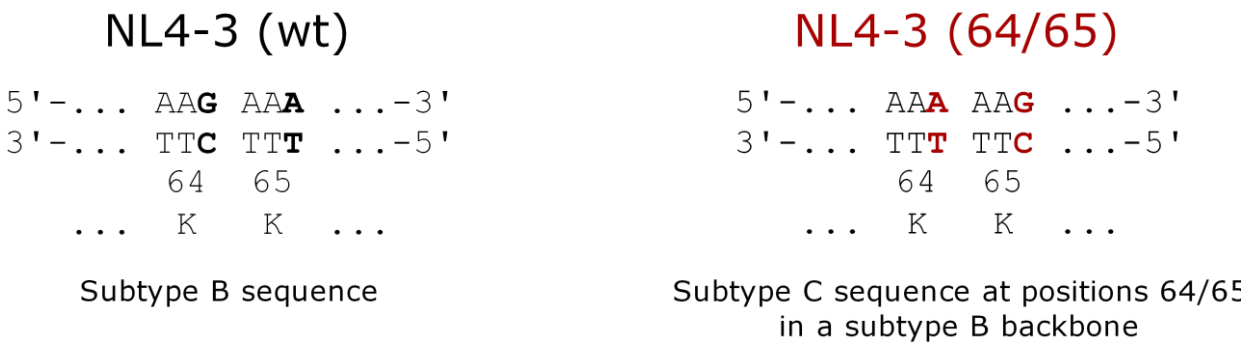
What is the propensity of different recombinant viruses to develop the K65R resistance mutation under N(t)RTI treatment ?



Infections of MT-2 cells and CBMCs with these viruses followed by treatment with different N(t)RTIs (single drugs or in combination).

Selections in CBMCs

Drugs	Virus			
	NL4-3 (wt)		NL4-3 (64/65)	
	Mutation	Week	Mutation	Week
TFV	none	>35	**K65R**	≈25
TFV + 3TC	M184V	≈15	**K65R**	≈20



The double mutant NL4-3 (64/65) acquires K65R more rapidly in CBMCs than wild-type NL4-3.

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**
TFV	None	None	None	**K65R**

Fortunately, the WHO has now disrecommended the use of stavudine (d4T) and Triamune (d4T/3TC/NVP) in HIV therapy

But, it is possible that millions of people already harbour K65R and will now have limited treatment options.

A recent study by Marconi et al (CROI, 2012) from South Africa suggests that this may be the case.

Should we have drug resistance concerns regarding the use of TDF/FTC in PreP, particularly in settings in which subtype C viruses are most prevalent?

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

- Bluma Brenner
- Hongtao Xu
- Dimitri Coutsinos
- Jerry Zaharatos
- Maureen Oliveira


MERCI