Induction/maintenance therapy : is there a scientific&virological rationale?

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Definitions

Induce/start treatment with three drugs and after a variable interval (6 months or longer) reduce the number of drugs, “maintain” virological suppression (“simplify”) to less (1/2) drugs

Genetic barrier "*to resistance*"

- Genetic barrier *to resistance* describes the number of mutations required to make the virus "resistant" e.g. more in vitro than in vivo definition.
- Depends largely on the drug concentration eg single mutation can cause resistance to a protease inhibitor but when the PI is boosted is not sufficient to cause virological failure
- Mutations causing resistance can affect replication of the virus then compensatory mutations may be required for virological failure to occur in vivo

Genetic barrier

Genetic barrier describes the total number of mutations required to lose (part of) it's CLINICAL activity.

1) Virus population

   - variability (size of the population and duration of infection)

2) Resistance profile

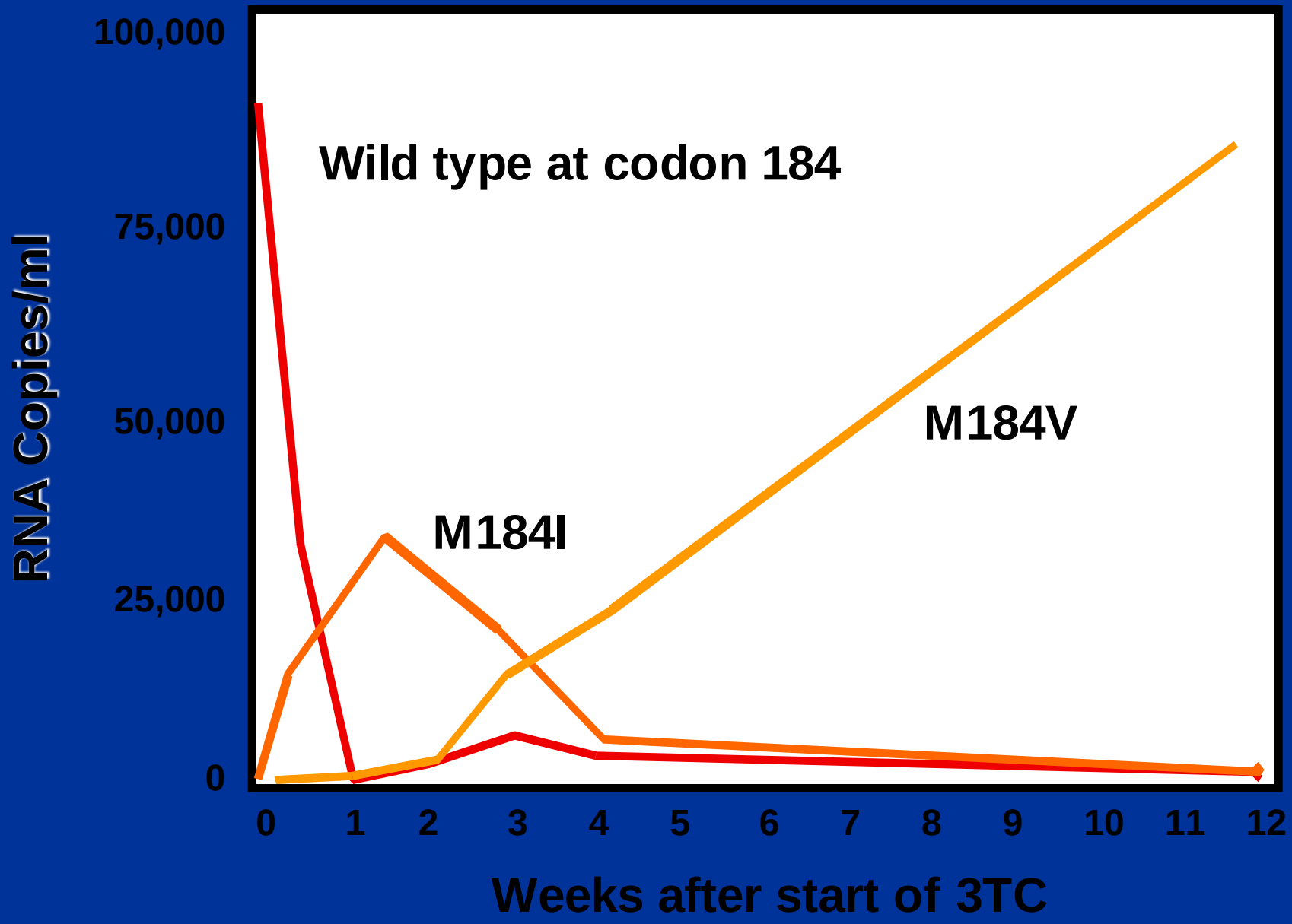
   - mechanism eg binding between target and inhibitor
   - concentration of the drug

3) Replicative activity: to what extent mutation

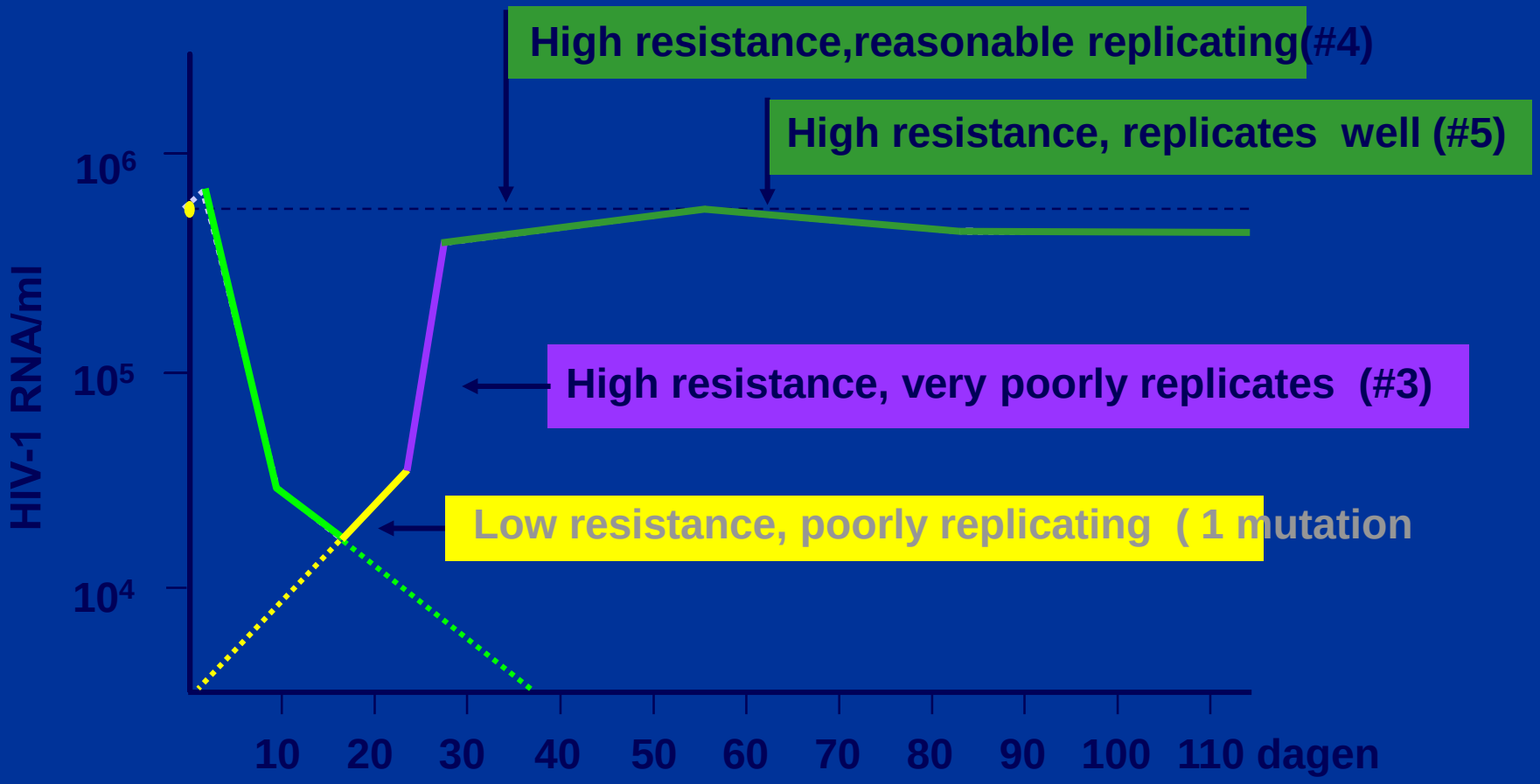
   - enzyme function/viral replication
   - compensation.

Rapid appearance of 3TC-Resistant Mutations inTreated Patients

Schuurman et al, JID 1995; 171:1411

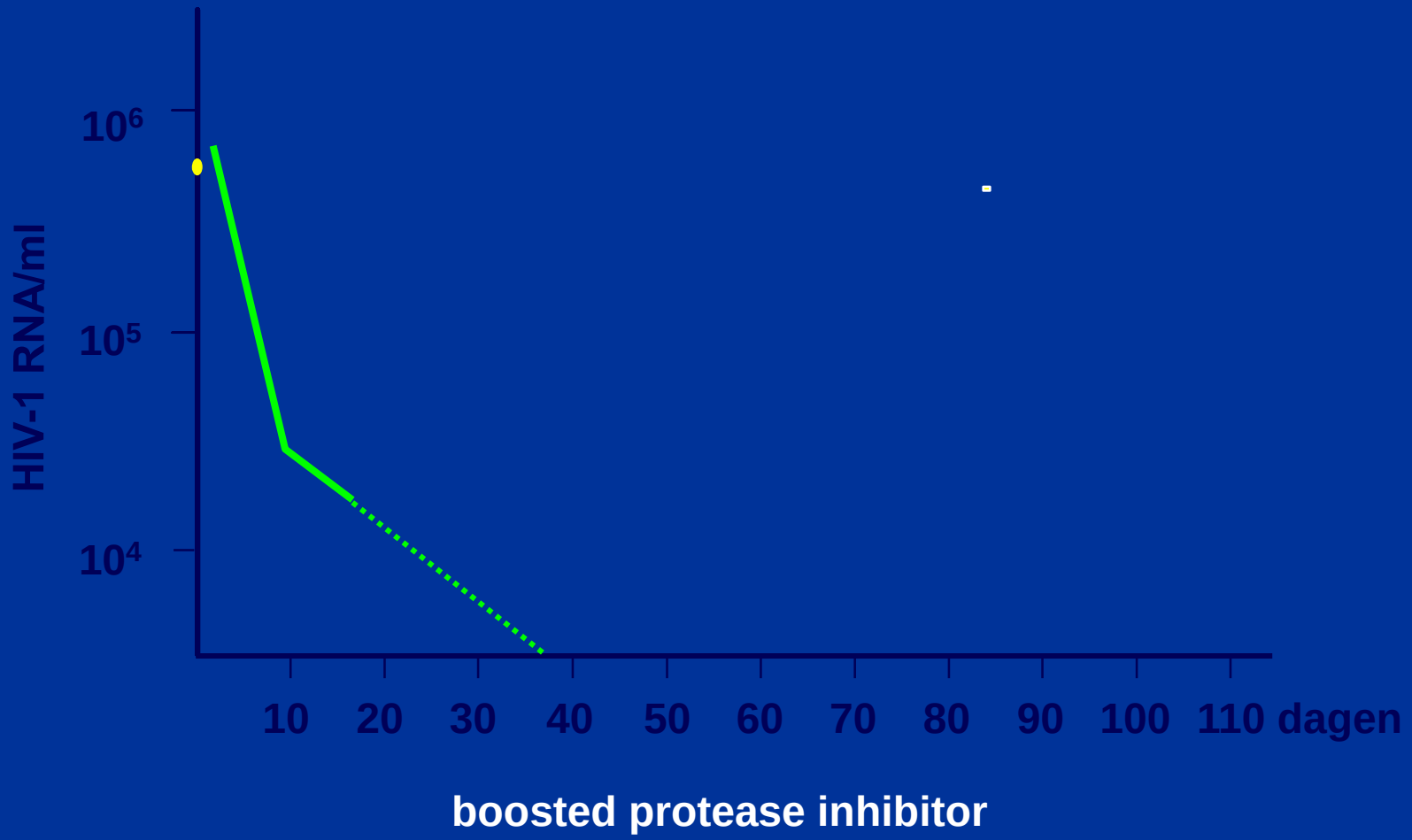


Evolution of resistance



mono therapy *non-boosted* protease inhibitor

Boosted PI


HIV-1 RNA/ml
10^6
10^5
10^4
10 20 30 40 50 60 70 80 90 100 110 dagen
boosted protease inhibitor

Genetic Barrier of Drug Classes

Drug Class	GB
NNRTI/NRTI	1
Protease inhibitors	1
Boosted PI	>3
First generation INSTI	-
Second generation INSTI	-

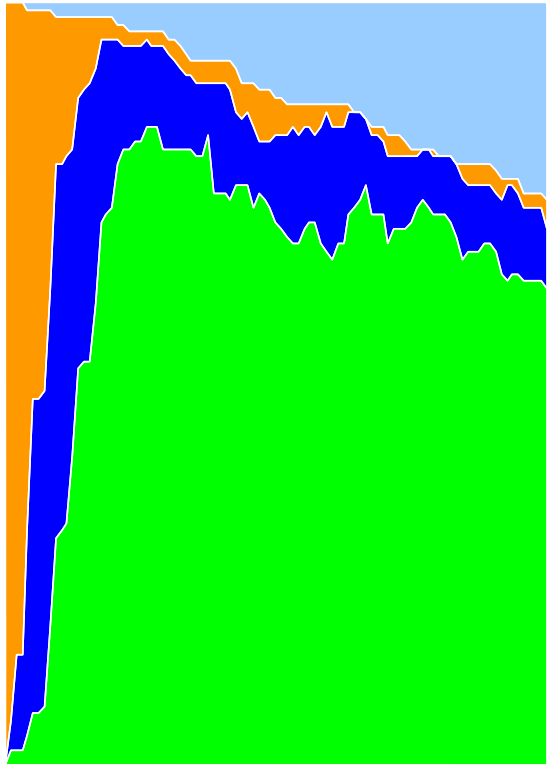
Development of HIV therapy

- First HAART regimens consisted of three drugs all with a genetic barrier of 1.
- These regimens (GB=3) suppressed viral replication in most of the individuals.
- However some of these triple regimens failed because of high viral load /increased viral variability and or cross resistance between the drugs the triple reducing the GB of that regimen

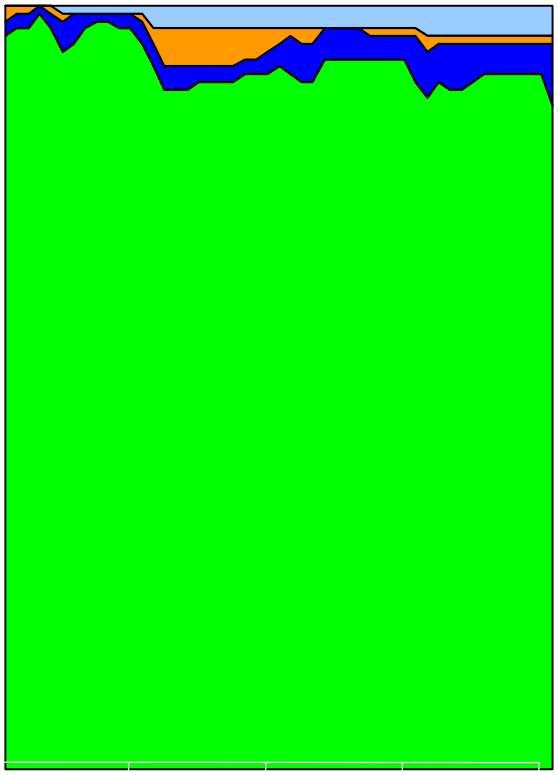
Monotherapy with LPV/r

MONARK – LPV/r
Initial therapy

Study 613 – LPV/r
Induction/maintenance



OK – LPV/r
Simplification



INSTI IN-VITRO RESISTANCE PROFILE

DTG (56 days)[1,2] FC = 1.2–4.1	RAL (84 days)[1,3,4] FC = 6 – >138	EVG (56 days)[1,3] FC = 2–497
S153F	**Q148K**	**T66I**
	Q148R	**E92Q**
	E138K/Q148K	**P145S**
DTG (84 days)[1,2] FC = 1.2–4.1	**E138K/Q148R**	**Q148K**
	G140S/Q148R	**Q148R**
S153Y	**N17S/Q148K/G163R**	**T66K**
	G140C/Q148K/G163R	**E92V**
S153F	**E138K/Q148K/G163R**	**P145S**
DTG (112 days)[1,2] FC = 1.2–4.1	**E92Q/E138K/Q148K/M154I**	**Q146L**
	N155H/I204T	**Q148R**
S153Y	**V151I/N155H**	**T66I/V72A/A128T**
S153F	**V151I/N155H**	**T66I/E92Q**
		T66I/Q146L

Integrase substitutions observed during passage of wild-type HIV-1 IIIB strain in the presence of DTG, RAL or EVG; list excludes polymorphisms. Mutations in **bold** indicate those seen in clinical trials

All substitutions observed during DTG passage had low level impact on DTG susceptibility (FC≤4.1)[1,2]

1. Adapted from Sato A, et al. IAS 2009. Poster WEPEA097 2. Data on file (Global Data Sheet) .3. Kobayashi M, et al. Antiviral Research 2008;80;213–22.4. Kobayashi M, et al. Antimicrob Agents Chemother 2011;55:813–21

Dolutegravir

Subtype	Virus	Baseline polymorphisms	Week 20				Week 37			
			DTG concentration (μM)	Acquired mutations			DTG concentration (μM)	Acquired mutations		
B	5331	I72V	0.05	R263K						
	BK-132	M154I, V201I	0.05	R263K		W243G/W	0.05	R263K		E138E/K
	5326	V72I, I203 M	0.05	R263K/R	S153Y	R166K/R	0.05		S153Y	
	PNL4.3	I72V, I113V, L234V	0.05	R263K		M50I/M, V151I	0.05	R263K		M50I, V151I
	12197 RAL TI WT for INI	I203 M	0.01	R263K		D288E	0.025	R263K (week 34)		D288E (week 34)
AG	6399	V72I, T125A, V201I	0.025		G118R	E69E/K	0.05		G118R	
	96USSN20	V72I, T125A, V201I	0.1	R263K			0.1	R263K		H51H/Y
C	4742	V72I, Q95P, T125A, V201I, I203 M	0.05		G118R		0.05		G118R	H51Y
	96USNG31	V72I, T125A, V201I	0.01		S153S/T		0.025			H51Y, G193E/G

[a] Baseline polymorphisms and acquired substitutions are indicated.

Quashie et al J virol 2012

EFFECT OF R263K IN IC_{50} USING SITE-DIRECTED MUTANTS

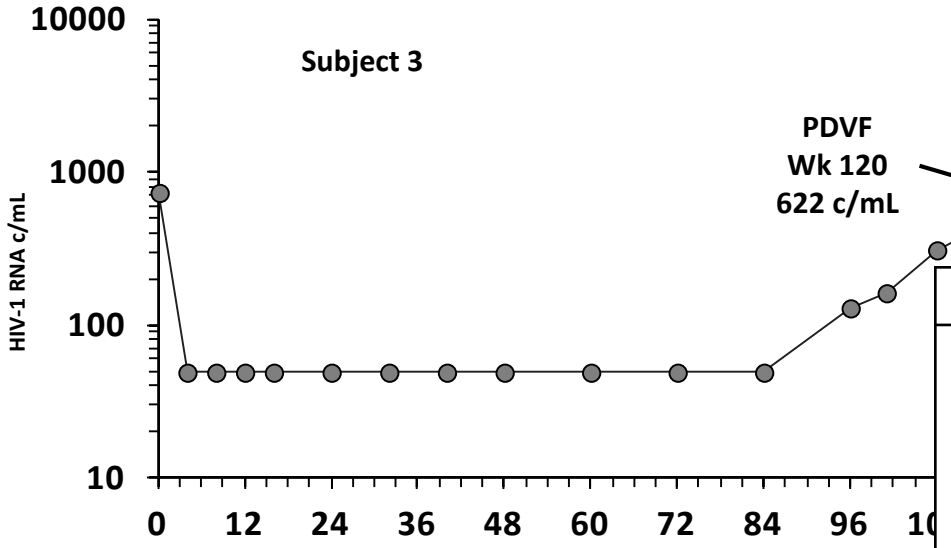
Strain	IN substitution / FC IC_{50}	DTG	RAL	EVG
NL432[a]	R263K	1.5	0.8	1.3
HXB2[b] RVA	V260I	1.0	0.7	5.3
	R263K	2.1	0.6	10.6
	V260I/R263K	2.0	0.5	6.3

- DTG and RAL retained activity against the R263K and V260I/R263K mutants

[a]HeLa-CD4 cells, 3-day assay, B-gal readout.
[b]MT4 cells, 5-day assay, cell titer glow readout

Subject 3: Virologic Characteristics

- Day 1: Clade B; PSS = 2, GSS = 2
- Regimen ($PSS_{Day\ 1}$): tenofovir (1) and emtricitabine (1)
- DTG C0[a]: Wk 4 = 0.36 µg/mL, Wk 24 = 0.22 ug/mL, **Wk 48 = 0.03 ug/mL**



	Day 1	PDVF	Confirm.
HIV-1 RNA	733	622	1054
IN mutation	-	A49G, S230R, R263K	A49G, S230R, R263K
DTG FC	0.73	3.82	5.77
RAL FC	0.54	2.39	2.62
IN RC*	20%	7.1%	12%

PDVF BR: No emergent resistance, and no NRTI resistance at any time points

[a] Geometric Mean Week 4 + Week 24 C0 0.86 µg/mL (CVb=140%)
[b] Could not be determined

- Decreased replication capacity with A49G,S230R,R263K substitutions

* Wildtype RC = 100%

Genetic Barrier of Drug Classes

Drug Class	GB
NNRTI/NRTI	1
Proease inhibitors	1
Boosted PI	>3
First generation INSTI	1
Second generation INSTI	>3

Virological rationale for “maintenance”

From a virological perspective simplification to a two drugs regimen with boosted PI+3TC or DTG +3TC, with one of the drugs in the combination (boosted PI/DTG) having a genetic barrier of three should be able to suppress viral replication in most individuals.

From a virological perspective it is the increased activity (GB) of these drugs allowing to use dual (mono) therapy.

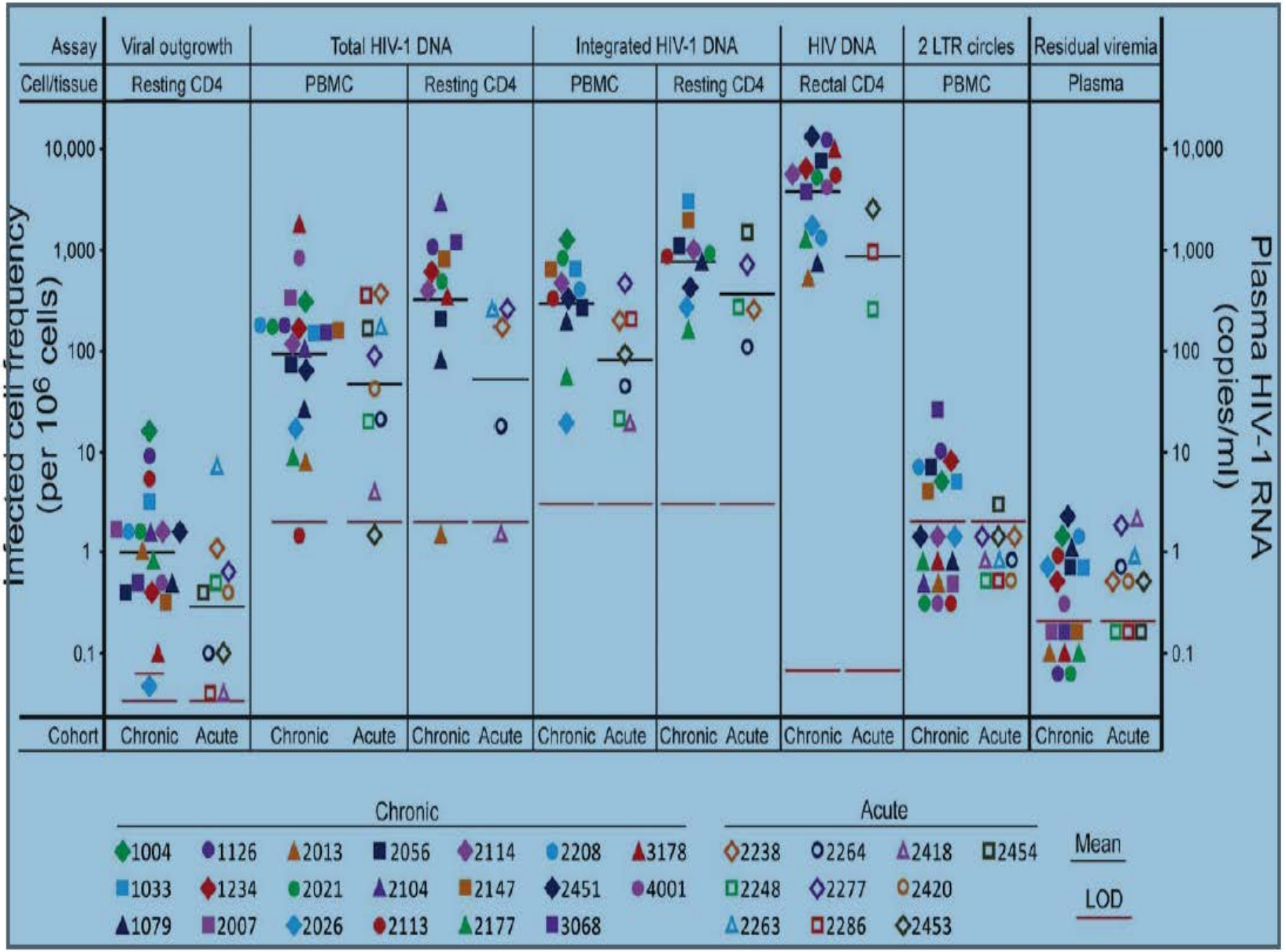
Two special patient populations

- Individuals starting therapy in the acute infection phase.

- Individuals on long term suppressive therapy.

Individuals starting therapy in the acute infection phase

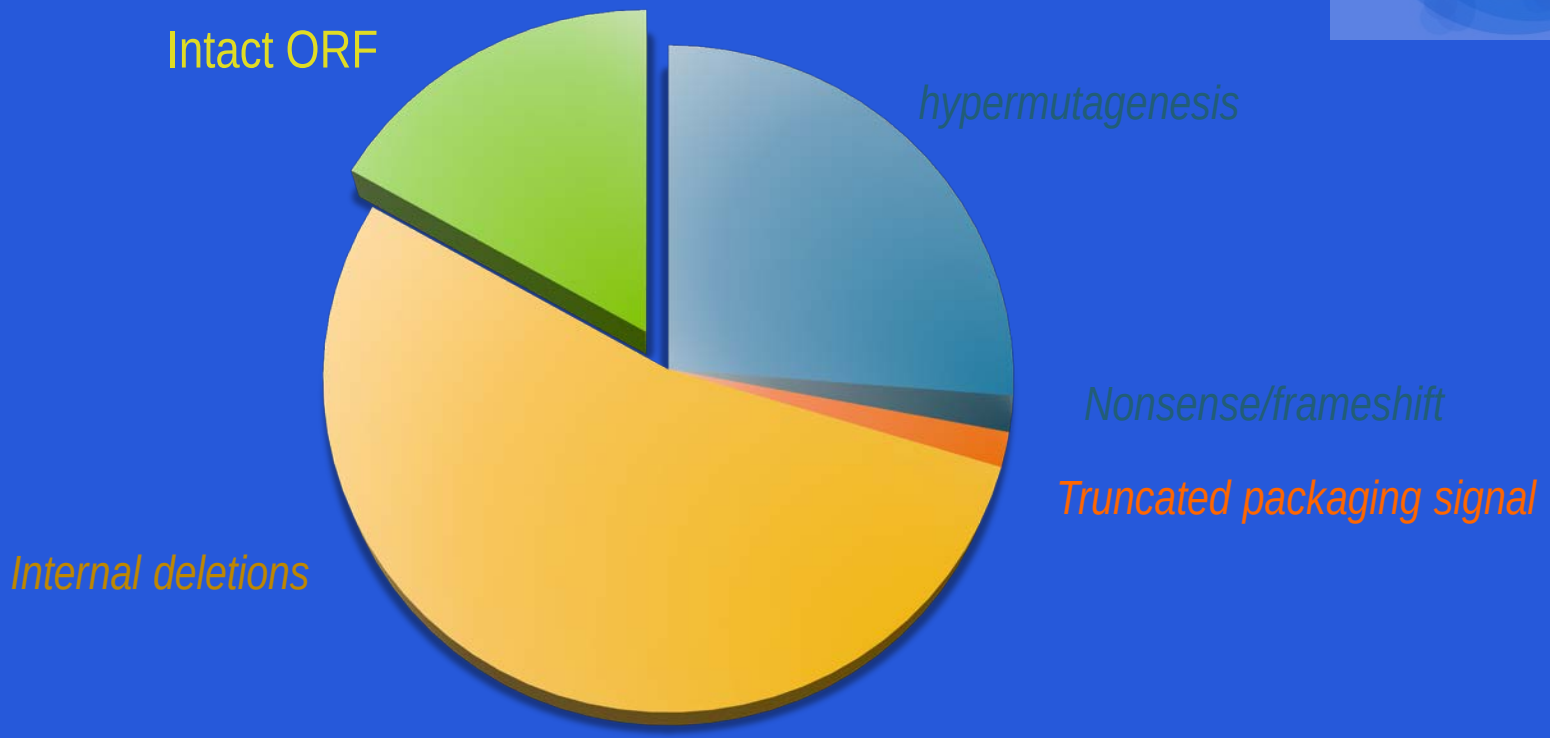
- The amount (and nature) of cells carrying (pro)virus is lower
- The variability of the (pro) viral population is reduced


Assay
Viral outgrowth
Total HIV-1 DNA
Integrated HIV-1 DNA
HIV DNA
2 LTR circles
Residual viremia
Cell/tissue
Resting CD4
PBMC
Resting CD4
PBMC
Resting CD4
Rectal CD4
PBMC
Plasma
Infected cell frequency (per 10^6 cells)
10,000
1,000
100
10
1
0.1
Plasma HIV-1 RNA (copies/ml)
Cohort
Chronic Acute
Chronic
1004 1126 2013 2056 2114 2208 3178
1033 1234 2021 2104 2147 2451 4001
1079 2007 2026 2113 2177 3068
Acute
2238 2264 2418 2454
2248 2277 2420
2263 2286 2453
Mean
LOD

Individuals on long term suppressive therapy

- The amount (and nature) of cells carrying (pro)virus is lower
- The variability of the (pro) viral population is reduced

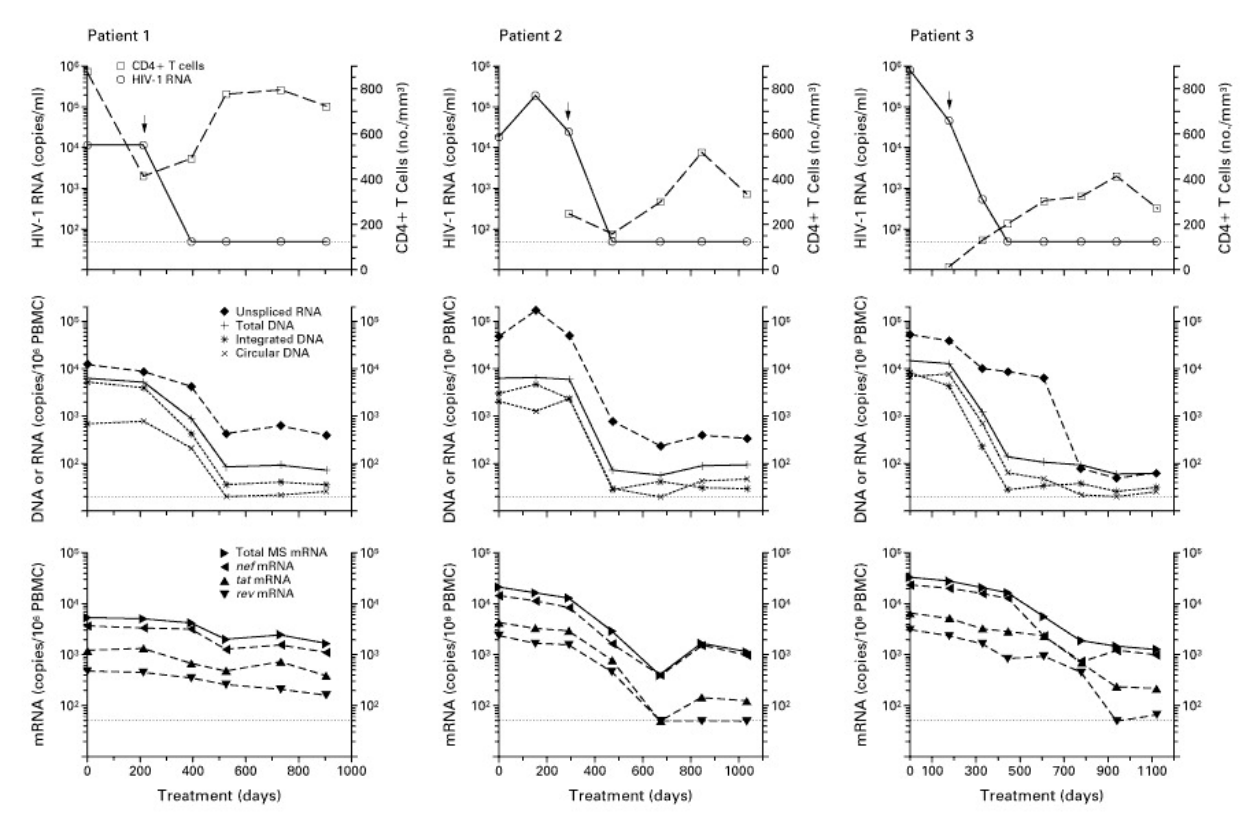
Characterization of non-induced HIV1 proviruses



J. Martines-Picado

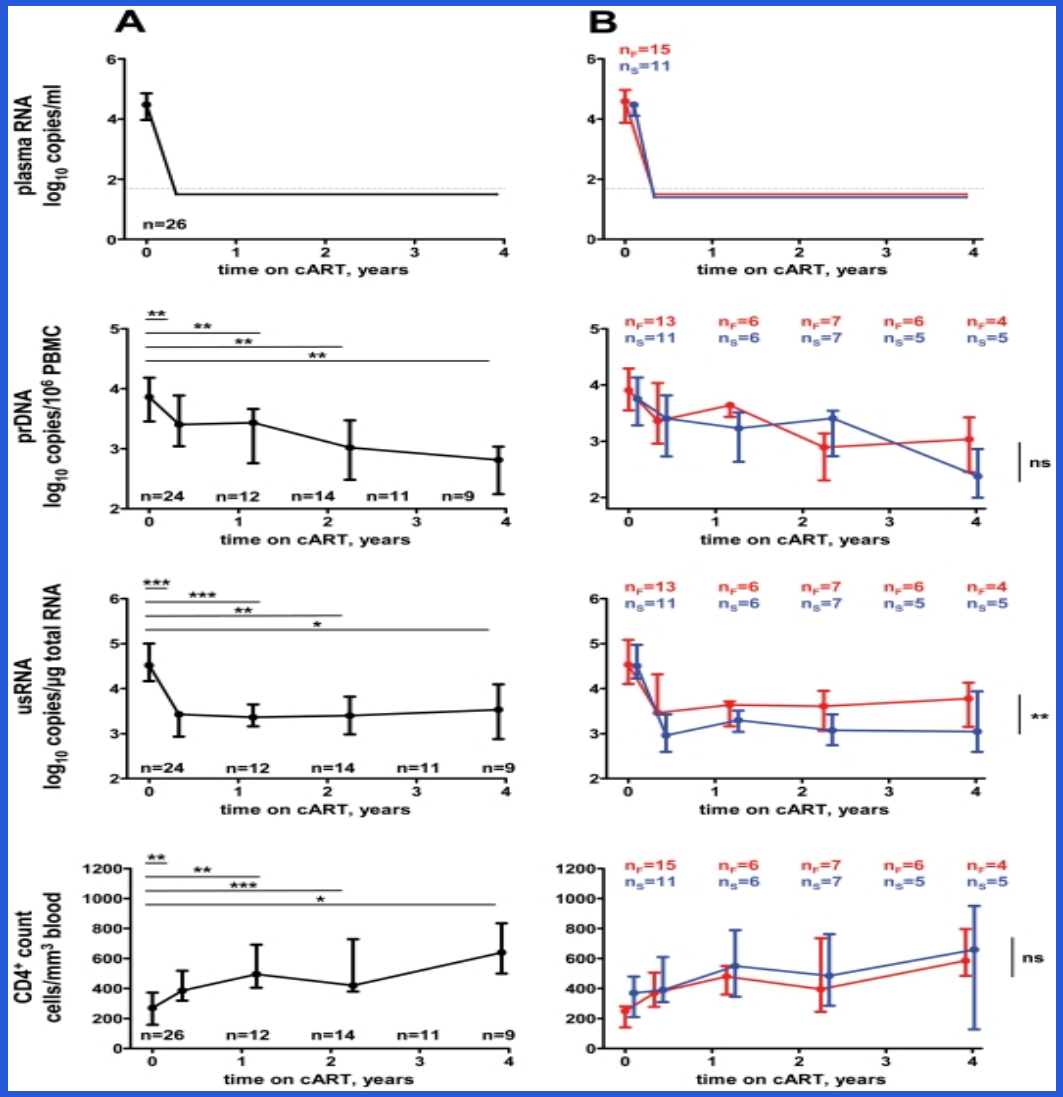
Ho et al. CROI 2013 (Abstract #43)

Amount CA HIVRNA pre/post cART



Furtado 1999 NEJM

Amount CA HIVRNA post cART



Pasternak 2009 PLoS ONE

- Red=failure
- Blue=success
- ** represents P<0.05

In theory: virological rationale for true maintenance (low GB) ART

- Lower total amount of effective provirus
- Less genetically diverse proviral population on cART
- No evidence of ongoing replication cycles and accumulating mutations

- .

Conclusion

Regimens consisting of one or two high genetic barrier drugs may be sufficient to keep someone suppressed, one can question whether the definition “maintenance” may apply

In theory in special populations the genetic barrier required for viral suppression may be reduced, however the clinical relevance may be limited