Erasmus MC

Viroscience lab

WHERE SKILLS MEET TO STUDY & PROTECT

Dynamics of HIV-1 resistance in patients treated with dolutegravir maintenance monotherapy

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Disclosure

	Companies/funders
Sponsoring or research fee	EU project EHVA (#681032)
Inventor on patent “Methods for determining antibiotic resistance in microorganisms” (15197806.1 – 1408 / 3023503)	Erasmus MC (patent holder), Bruker Daltonics (licence)

Results randomized controlled DOMONO-study on DTG maintenance monotherapy

- **DOMONO main study[1]**
- Inclusion: viral suppression for at least 6 months, CD4 nadir **above** 200, HIV-RNA zenith < 10^5 c/mL, no previous virological failure and/or documented RAMs
- DTG 1dd 50 mg po
- **8**/95 patients virological failure

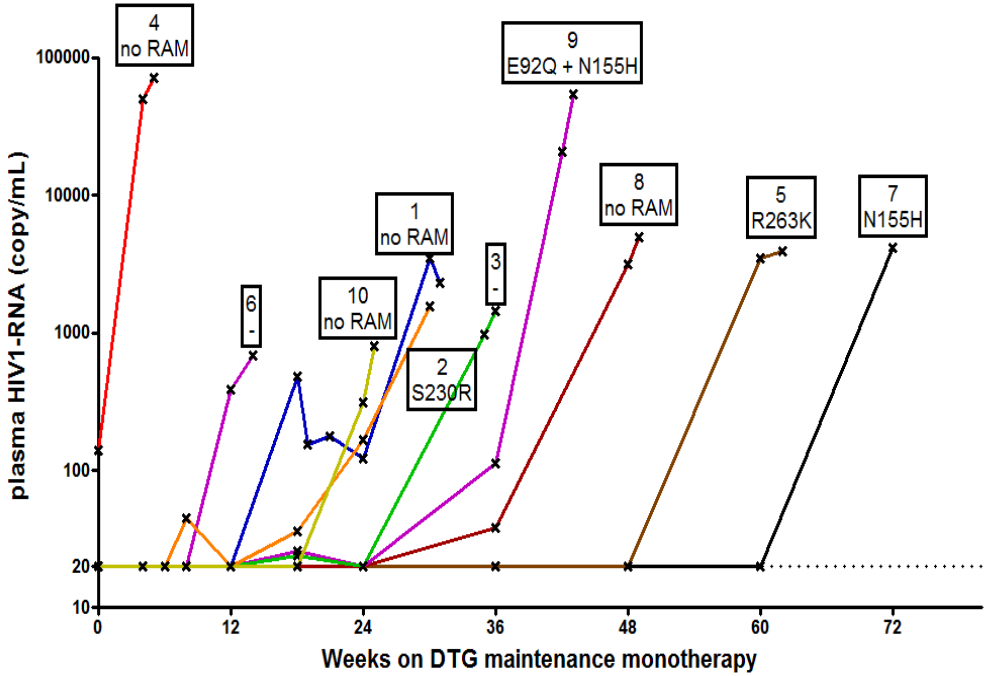
- **Pilot study**
- Inclusion criteria same as main study except CD4 nadir **below** 200
- DTG 1dd 50 mg po
- **2**/4 patients virological failure

- **This study**
- Describe dynamics of resistance in the 10 patients who failed DTG maintenance monotherapy

[1] Wijting et al., Lancet HIV, 2017

Baseline characteristics

	Patients (N=10)
Male sex, N (%)	10 (100)
Age (years), median (Q1,Q3)	46 (39,52)
Mode of transmission, N (%)	
MSM	7 (70)
HSX	2 (20)
Other	1 (10)
Ethnicity, N (%)	
Caucasian	7 (70)
Caribbean/Surinam	3 (30)
Time on cART, median (Q1, Q3), months	71 (47, 104)
Time suppressed on cART, median (Q1, Q3), months	61 (41, 101)
INSTI-naive, N (%)	9 (90)
HIV-1 subtype B, N (%)	10 (100)
HIV-RNA zenith, median (Q1, Q3), c/ml	29,750 (18,250, 66,625)
CD4 T-cell nadir, median (Q1, Q3), cells/mm^3	235 (183, 300)



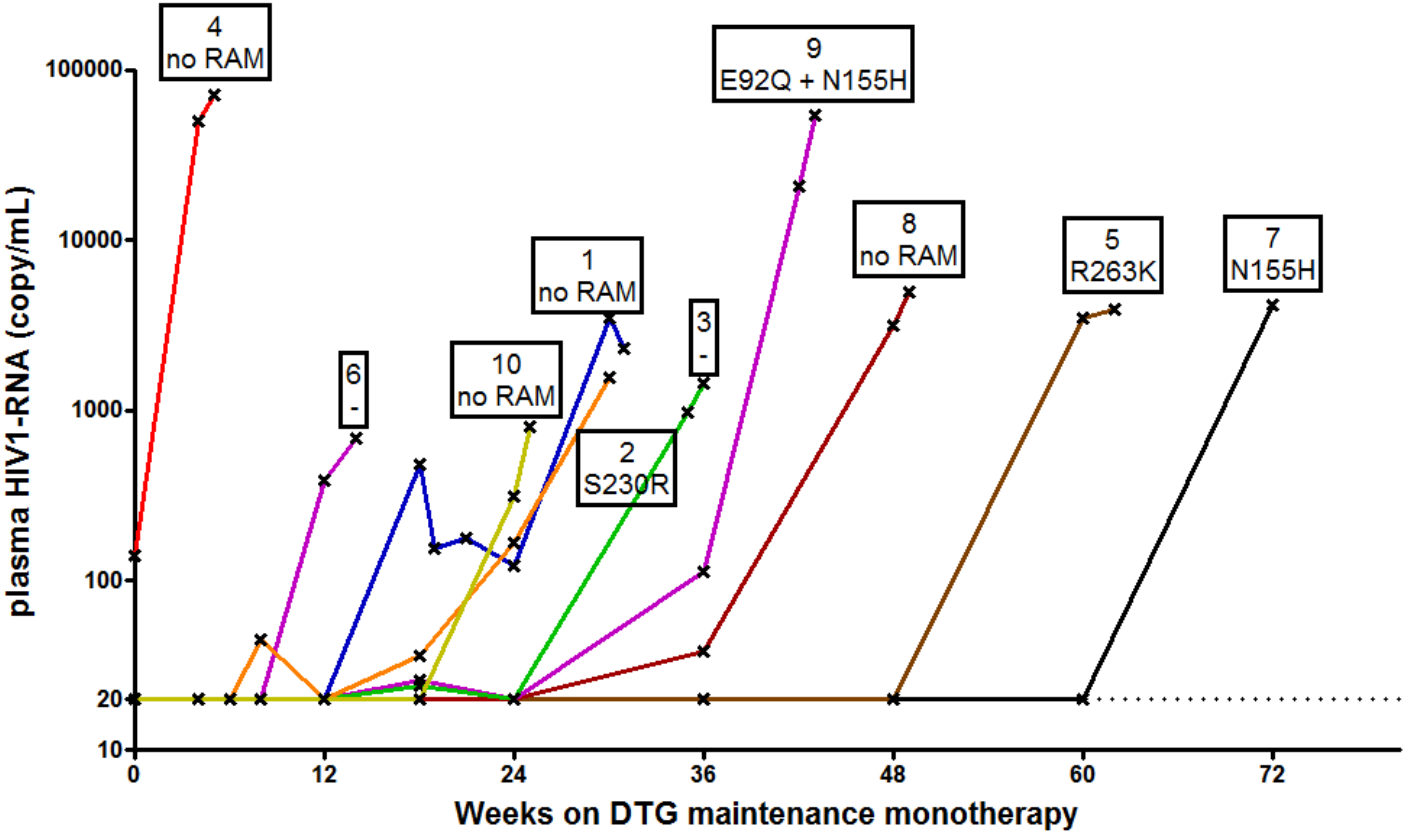
Patient	HIV-RNA zenith (c/ml)	DTG-plasma level at VF (mg/L)	adherence	INSTI-RAM at VF	Fold change IC_{50} DTG in literature[1-4]
4	18.500	1.29 (+14h)	>95%	No	-
6	7.420	2.00 (+19h)	>95%	-	-
10	66.500	5.31 (+19h)	>95%	No	-
1	17.500	2.59 (+16h)	>95%	No	-
2	99.270	2.96 (+22h)	>95%	S230R	4
3	56.300	1.00 (+24h)	>95%	-	-
9	24.900	0.86 (+16)	>95%	E92Q + N155H	2.5
8	67.000	1.44 (+24h)	>95%	No	-
5	34.600	0.70 (+13h)	>95%	R263K	2 - 4
7	20.100	2.15 (+9h)	>95%	N155H	1 - 2

[1] Kobayashi et al., Antimicrob Agents Chemother, 2011. [2] Wainberg et al., J Virus Erad, 2015. [3] Underwood et al., J Acquir Immune Defic Syndr , 2012. [4] Pham et al., in preparation

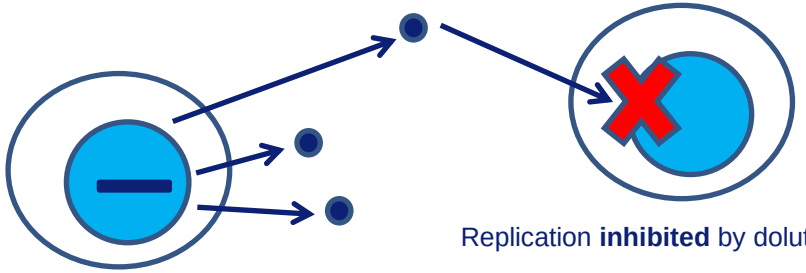
Genetic barrier to DTG resistance

- N155H, E92Q + N155H, R263K, S230R → 1-4 fold change in IC_{50} of DTG *in vitro*
- Single INSTI-RAMs conferring low level resistance *in vitro* are sufficient to cause virological failure in DTG maintenance monotherapy
- Genetic barrier to DTG resistance too low to justify maintenance monotherapy
- Cross resistance with other INSTIs

Large variation in time to virological failure

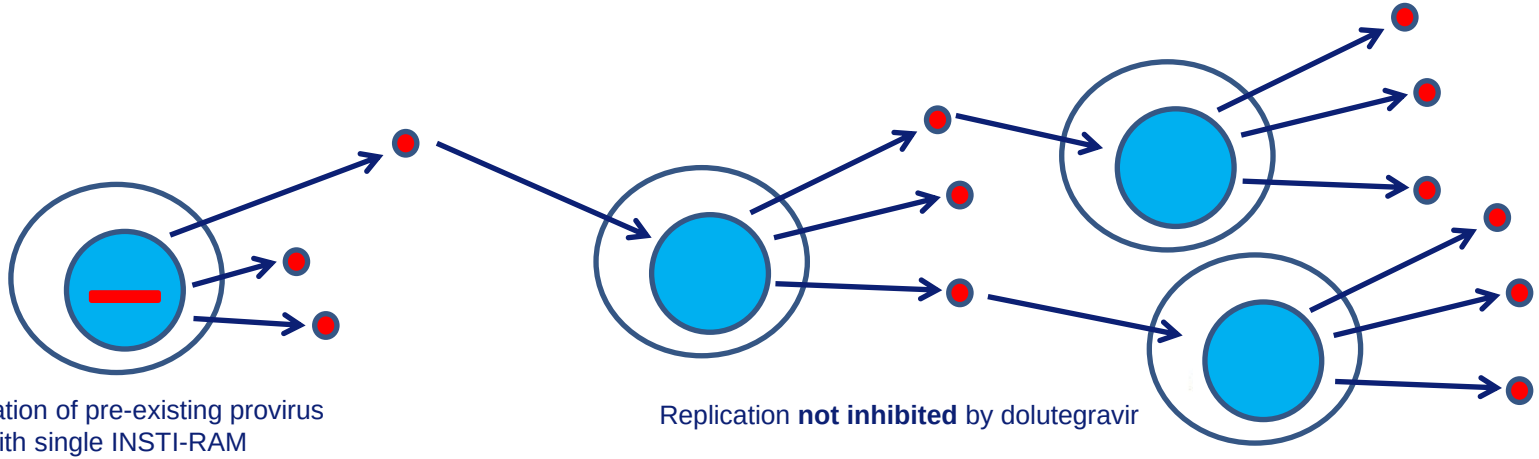


Stochastic reactivation of a provirus with single INSTI-RAM?



Reactivation of susceptible provirus

Replication **inhibited** by dolutegravir



Reactivation of pre-existing provirus with single INSTI-RAM

Replication **not inhibited** by dolutegravir

Novel INSTI resistance mechanism?

- *In vitro* selection experiments with high DTG concentrations → mutations in 3'-polypurine tract causing high level INSTI resistance[1]

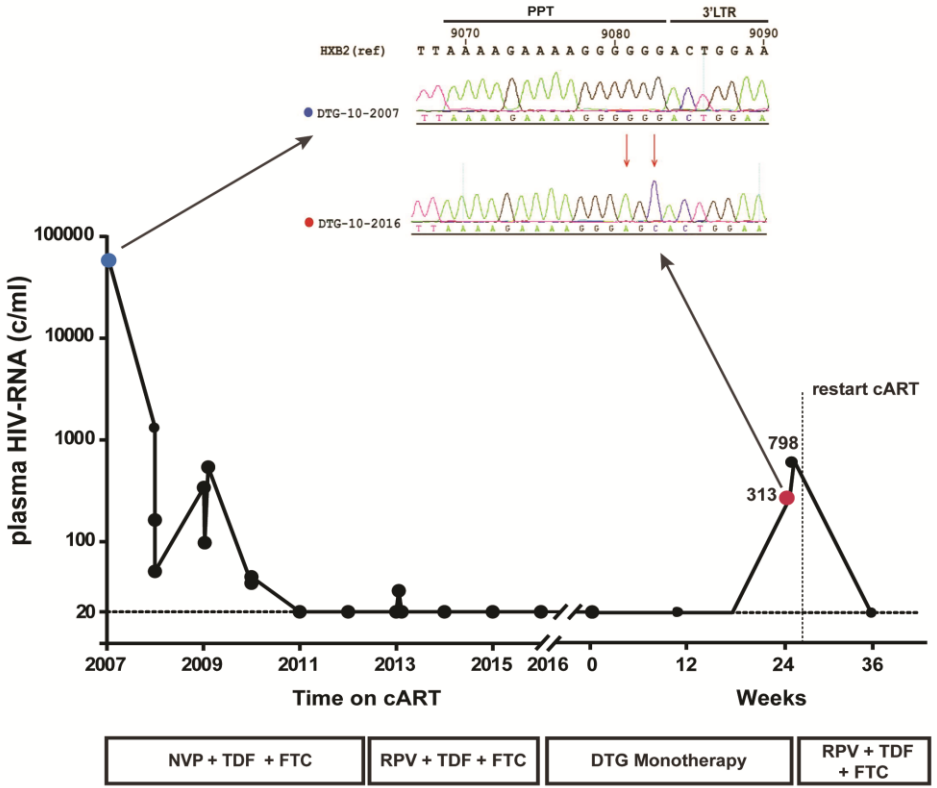
- 3'-polypurine tract is > 99.9% conserved in HIV-1 sequences in the Los Alamos database

- We sequenced all patients with VF (pre-cART and at VF) → one patient (#10) developed changes in 3'-polypurine tract during VF

[1] Malet et al., mBio, 2017

First patient failing on INSTI with emergence of changes in 3'-polypurine tract

	3' polypurine tract (PPT)														LTR			
HXB2_ref	A	A	A	A	G	A	A	A	A	G	G	G	G	G	G	A	C	T	G
9053 Lai*	A	A	A	A	G	A	A	A	A	G	C	A	G	T	-	A	C	T	G
Pat 1	A	A	A	A	G	A	A	A	A	G	G	G	G	G	G	A	C	T	G
Pat 3	A	A	A	A	G	A	A	A	A	G	G	G	G	G	G	A	C	T	G
Pat 4	A	A	A	A	G	A	A	A	A	G	G	G	G	G	G	A	C	T	G
Pat 6	A	A	A	A	G	A	A	A	A	G	G	G	G	G	G	A	C	T	G
Pat 8	A	A	A	A	G	A	A	A	A	G	G	G	G	G	G	A	C	T	G
Pat 10	A	A	A	A	G	A	A	A	A	G	G	G	A	G	C	A	C	T	G



See also poster P12 from C. Lungu

Conclusions

- Genetic barrier to resistance of DTG too low to justify maintenance monotherapy
- DTG monotherapy failure caused by viruses with INSTI-RAMs that confer cross resistance to INSTIs
- Stochastic reactivation of proviruses with single INSTI-RAM may explain virological failure
- Mutations in 3’-polypurine tract may lead to INSTI resistance *in vivo*

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