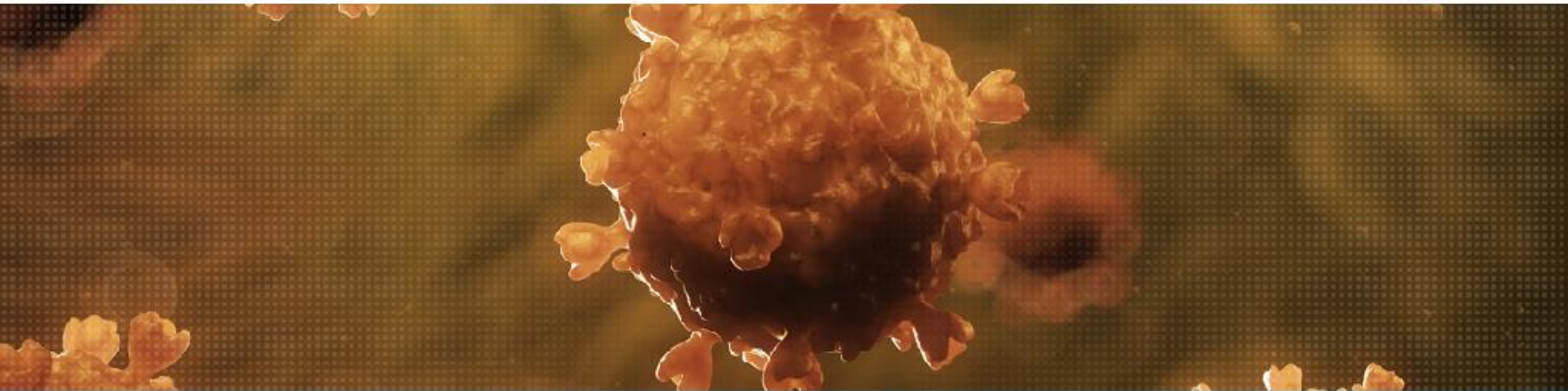


Erasmus MC



**Viroscience lab**

WHERE SKILLS MEET TO STUDY & PROTECT



**Mutations in the 3'-polypurine tract of HIV-1 point to a new integrase strand transfer inhibitor (INSTI) resistance mechanism in vivo.**

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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)

# In depth analysis of virologic failure in the DOMONO study

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**DOMONO study:** randomized trial on DTG (1dd 50 mg) maintenance monotherapy.

## **DOMONO main study (Wijting et al, Lancet HIV, 2017)**

Inclusion: viral suppression for at least 6 months, CD4 nadir **above** 200, HIV-RNA zenith  $< 10^5$  c/mL, no previous virologic failure and/or documented RAMs  
8/95 patients virologic failure  
DTG maintenance monotherapy inferior to cART and should not be used

## **Pilot study**

Inclusion criteria same as main study except CD4 nadir **below** 200  
2/4 patients virologic failure

## **This study (Wijting et al, JID, 2018)**

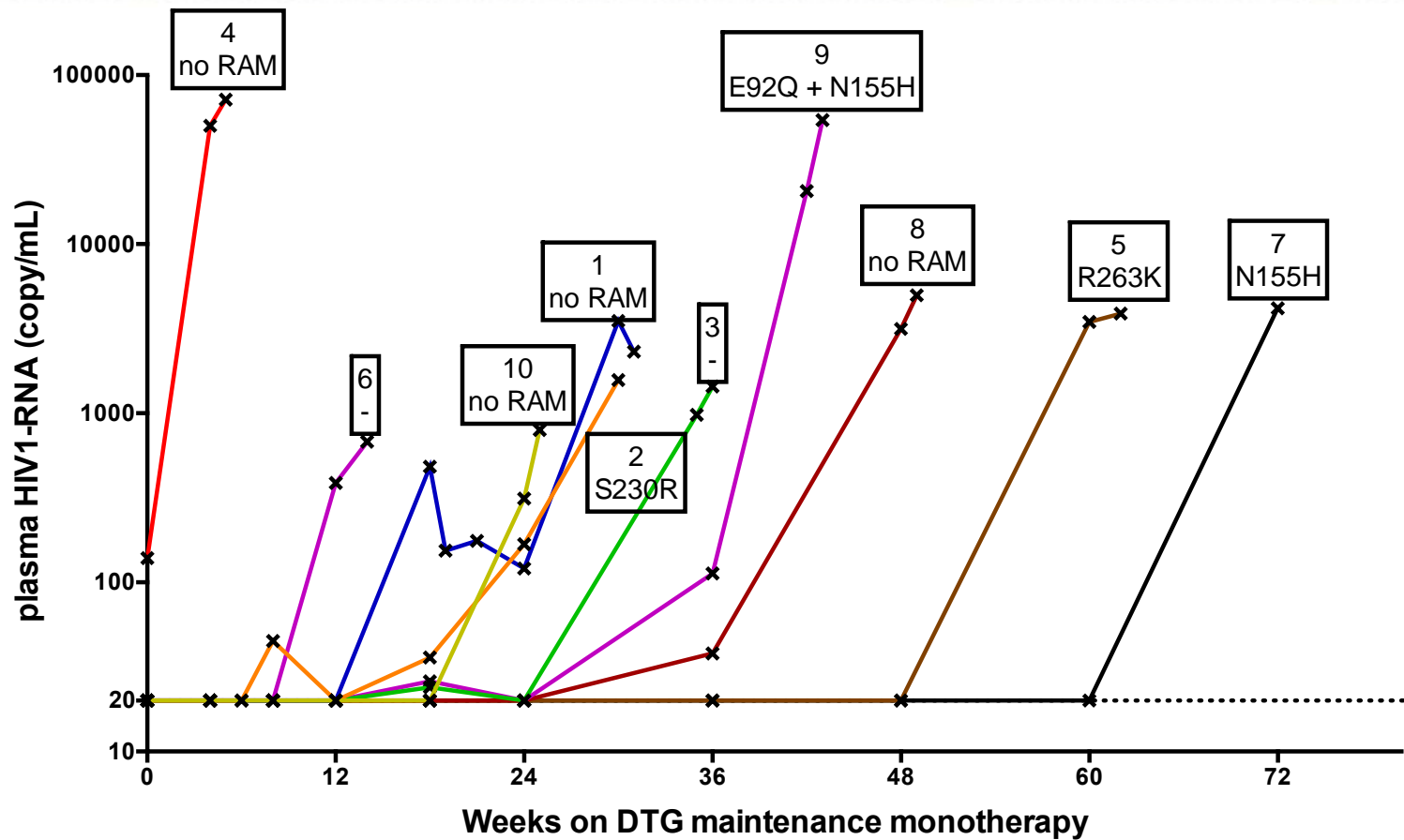
Describe dynamics of resistance in the 10 patients who failed DTG maintenance monotherapy

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# Baseline Characteristics

Characteristic	Patients (n = 10)
Male sex	10 (100)
Age, y	46 (39–52)
Mode of transmission	
Male-male sex	7 (70)
Heterosexual sex	2 (20)
Other	1 (10)
Ethnicity	
White	7 (70)
Caribbean/Surinam	3 (30)
Duration of cART, mo	71 (47–104)
Duration of cART-associated virologic suppression, mo.	61 (41–101)
INSTI naive	9 (90)
HIV-1 subtype B	10 (100)
Peak HIV-1 RNA load, copies/mL	29 750 (18 250–66 625)
Nadir CD4 <sup>+</sup> T-cell count, cells/mm <sup>3</sup>	235 (183–300)

Data are no. (%) of participants or median value (interquartile range)



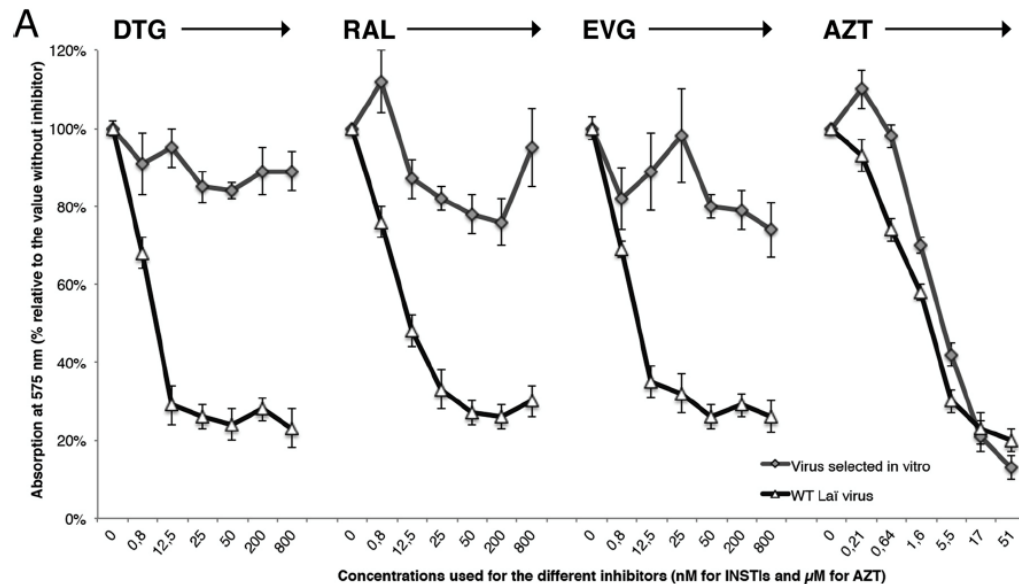
	4	6	10	1	2	3	9	8	5	7
DOMONO study	main	main	pilot	main	main	main	pilot	main	main	main
adherence	> 95%	> 95%	> 95%	> 95%	> 95%	> 95%	> 95%	> 95%	> 95%	> 95%
DTG level at VF	1.29 (+14h)	2.00 (+19h)	5.31 (+19h)	2.59 (+16h)	2.96 (+22h)	1.00 (+24h)	0.86 (+16h)	1.44 (+24h)	0.70 (+13h)	2.15 (+9h)
INSTI-RAM	no	-	no	no	S230R	-	E92Q + N155H	no	R263K	N155H

# Novel INSTI resistance mechanism?

Malet et al., CROI, 2017 & Malet et al., mBio, 2017:

*In vitro* selection experiments with WT Lai virus under high DTG concentrations

- High level resistance to INSTIs
- No resistance mutations in integrase
- 5 mutations in Nef region
  - 1 mutation 6 nucleotides upstream of the 3'-polypurine tract (3'-PPT)
  - 3 mutations + 1 deletion in the 3'-PPT



	3' polypurine tract (PPT)														
HXB2_ref	A	A	A	A	G	A	A	A	A	G	G	G	G	G	G
9053 Lai*	A	A	A	A	G	A	A	A	A	G	C	A	G	T	-

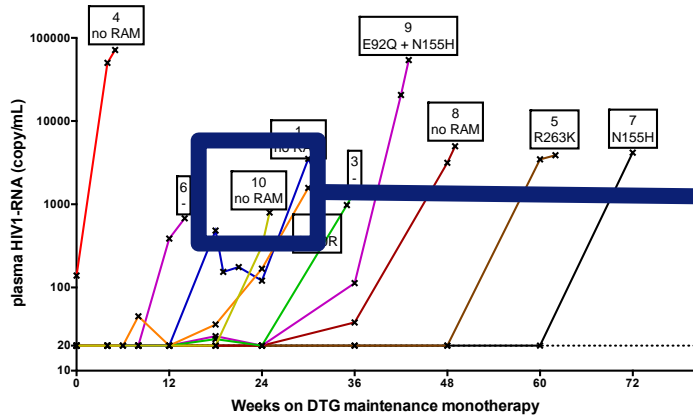
# This study

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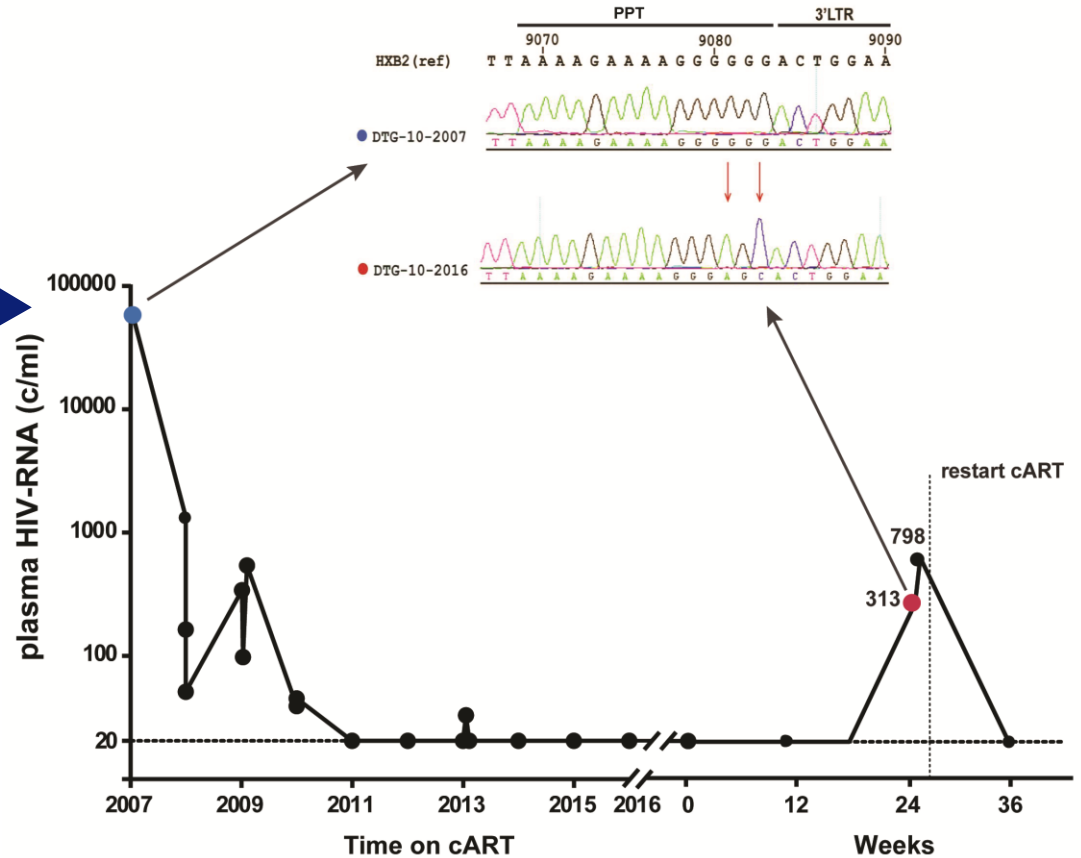
- Sanger sequencing of 3'-PPT in all 10 patients with VF
  - Pre-cART plasma samples
  - Plasma samples during virologic failure

**One patient (#10) developed changes in 3'-polypurine tract during VF**

# First patient failing on INSTI with development of mutations in 3'-PPT



No INSTI-RAMs detected!



	3' polypurine tract (PPT)														
HXB2_ref	A	A	A	A	G	A	A	A	A	G	G	G	G	G	G
9053 Lai*	A	A	A	A	G	A	A	A	A	G	C	A	G	T	-

Pat 10	A	A	A	A	G	A	A	A	A	G	G	G	A	G	C
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# Conclusions & Discussion

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- Mutations in 3'-PPT may cause INSTI resistance in vivo
  - Further proof with site directed mutant needed!
  
- Do 3'-PPT mutations explain VF in other patients treated with INSTI?
  - Further studies needed:
    - Case-control study
      - Cases: VF on INSTI-containing cART and no INSTI-RAMs
      - Controls: VF on non-INSTI-containing cART
    - Global DTG failure registry coordinated by ESAR (see [www.esar-society.eu](http://www.esar-society.eu))
  
- What is the mechanism of 3'-PPT mediated INSTI resistance?
  - Replication of unintegrated virus? (Malet et al, mBio, 2017)
  - Substrate change? (Wijting et al, JID, 2018; Das & Berkhout, mBio, 2018)
  - Other?

# Acknowledgements

- **All patients who participated in this study**
- **Viroscience, Erasmus MC**
  - Charles Boucher
  - Rob Gruters
  - Cynthia Lungu
  - David van der Vijver
  - Patrick Boers
  - Suzan Pas
  - Jolanda Voermans
- **Internal Medicine, Erasmus MC**
  - Bart Rijnders
  - Ingeborg Wijting
  - Ineke van der Ende
- **McGill University AIDS Centre, Canada**
  - Mark Wainberg
  - Thibault Mesplede
  - Hanh Pham
- **Virology, UMC Utrecht**
  - Rob Schuurman

