French national survey of resistance to integrase inhibitors shows high differences of resistance selection rate in case of virological failure in a context of routine hospital care (ANRS AC11 virology network)

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Objectives of the study

- Primary objective:
  - To characterize resistance patterns in case of virological failure to integrase inhibitor-based regimen in clinical setting from the french ANRS network

- Secondary objectives:
  - To identify factors associated with selection of INI resistance mutations
  - To identify new INI associated resistance mutations

Patients and methods

- **Inclusion criteria**
  - HIV-1 infected patient
  - Failing an integrase inhibitor-based regimen (RAL, EVG, DTG)
  - Virological failure confirmed if 2 consecutive plasma **VL ≥ 50 cp/ml** (01/01/2014 – 31/12/2017)
  - Patients followed in clinical sites within the ANRS AC11 resistance sentinel network

- **Genotypic resistance**
  - The sequences of the protease, reverse transcriptase (RT) and integrase genes were performed in each Virology laboratory, using the ANRS consensus technique.
  - Resistance tests were interpreted according to the last ANRS genotypic algorithm **(http://www.hivfrenchresistance.org)**

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GENOTYPE INTERPRETATION: INTEGRASE STRAND TRANSFER INHIBITORS

	Mutations associated with resistance	Mutations associated with « possible resistance »
RAL	• T66K [10] • E92Q [1, 2] • G118R [10, 17] • F121Y [10,17] • G140A/S [7] • Y143A/C/G/H/R/S [1, 3, 4, 5, 8, 14] • Q148E/G/H/K/R [1, 2] • V151L [9] • N155H/S/T [1, 2, 9] • E157Q [2] • A49G + S230G/R + R263K [18]	
EVG	• T66I/A/K [6] • E92Q [6] • T97A [21,22] • G118R [17] • F121Y [9,17] • E138K • G140C/S • Y143A/C/G/H/R/S [14] • P145S [9] • S147G [21] • Q148H/R/K [6] • V151L [9] • N155H/S/T [6,9] • E157Q [11] • R263K [18]	

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DTG* 50 mg BID	• G118R [12,13] • F121Y [17] • V151L [9] • S153Y [9] • R263K [16] • T66K + L74M [9] • E92Q + N155H [9, 23, 24] • Q148H/K/R + at least 2 mutations among: L74I or E138A/K/T or G140A/C/S [15] • Q148R + N155H [9]	• T66K [9] • S153F [9] • E157Q [19, 20] • Q148H/K/R + 1 mutation among: L74I or E138A/K/T or G140A/C/S [15]
50 mg QD	• G118R [12,13] • F121Y [17] • E138A/K/T • G140A/C/S • Q148H/K/R • V151L [9] • S153Y [9] • N155H [18] • R263K [16] • T66K + L74M [9]	• T66K [9 • S153F [9] • E157Q [19, 20]
CBG	• Q148K/R [25, 26, 27]	

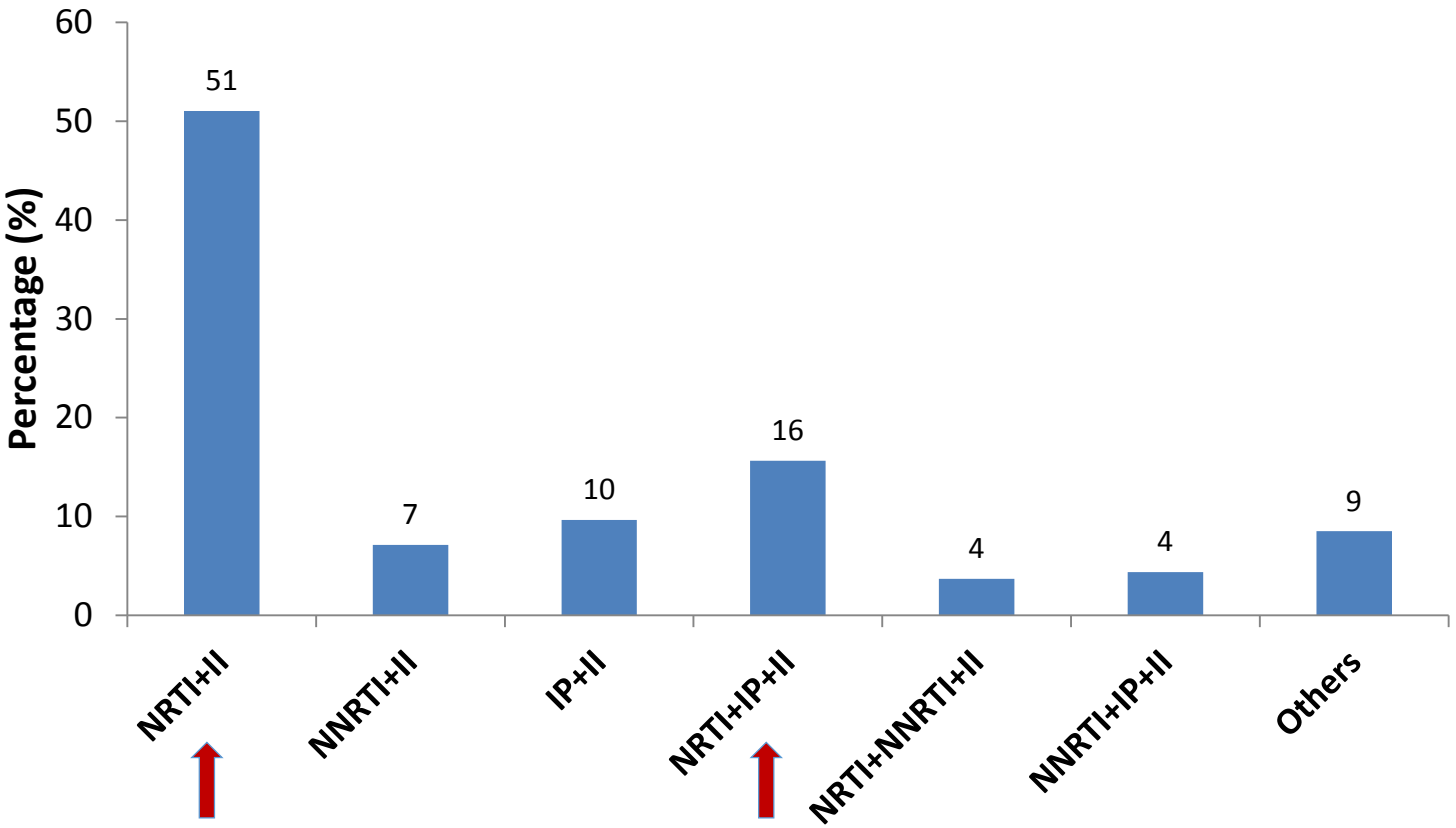
RAL: raltegravir, EVG: elvitegravir, DTG: dolutegravir, CBG: cabotegravir

* Please note that rules are different for DTG 50 mg BID and 50 mg QD

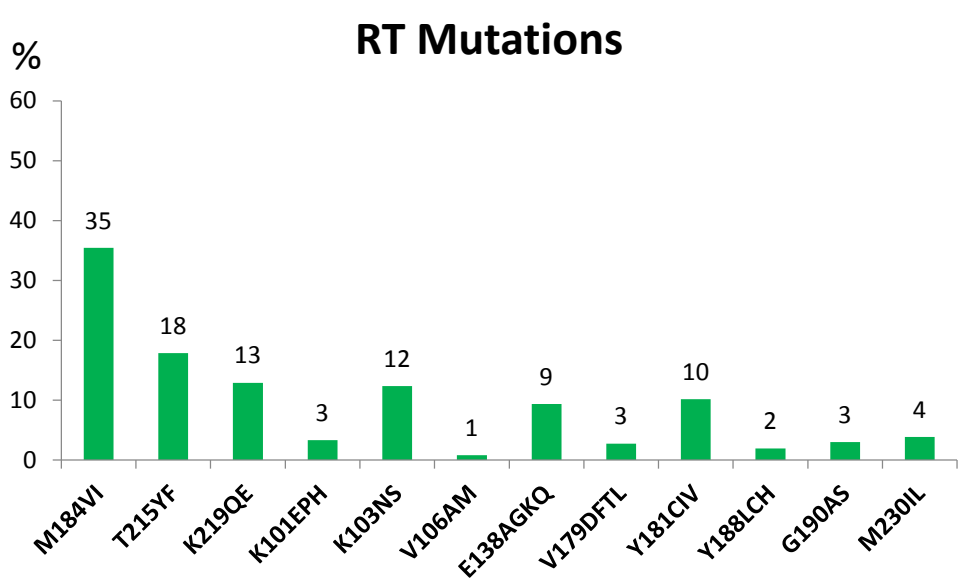
Population characteristics (n = 439)

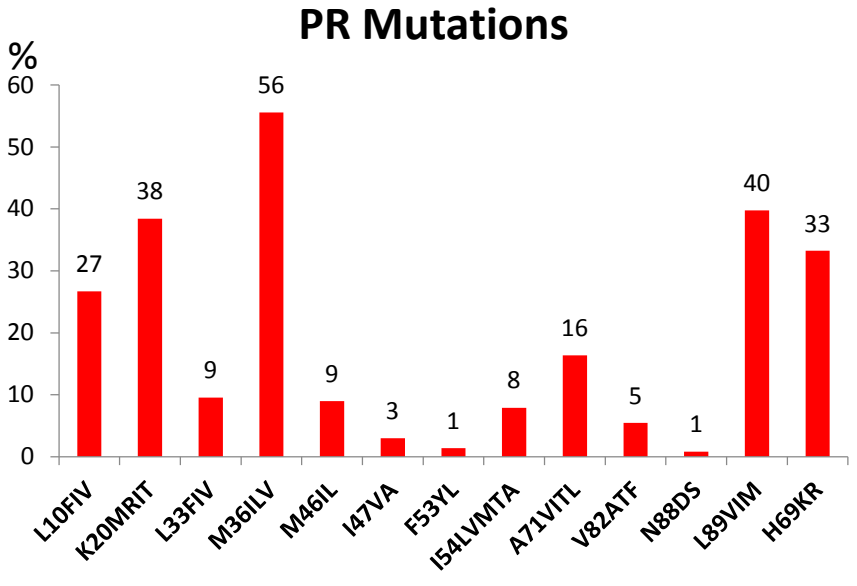
Variable	Median (IQR)
Age, years	48.6 [39.9-55.4]
Sex, male (%)	289 (66)
Time since HIV-1 diagnosis, years	17 [7.62-22.6]
Duration of current INI regimen ,years	0.9 [0.5-2.8]
Nadir CD4 cell count, mm^3	128 [31-283]
CD4 cell count at initiation, mm^3	364 [155-629]
CD4 cell count at failure, mm^3	386 [199-657]
viral load at initiation (Log_{10} cp/ml)	3.1 [1.8-4.8]
viral load at failure (Log_{10} cp/ml)	3 [2.3-4.0]
HIV-1 subtype B (%)	244 (56)

ARV treatment at time of failure (n = 439)

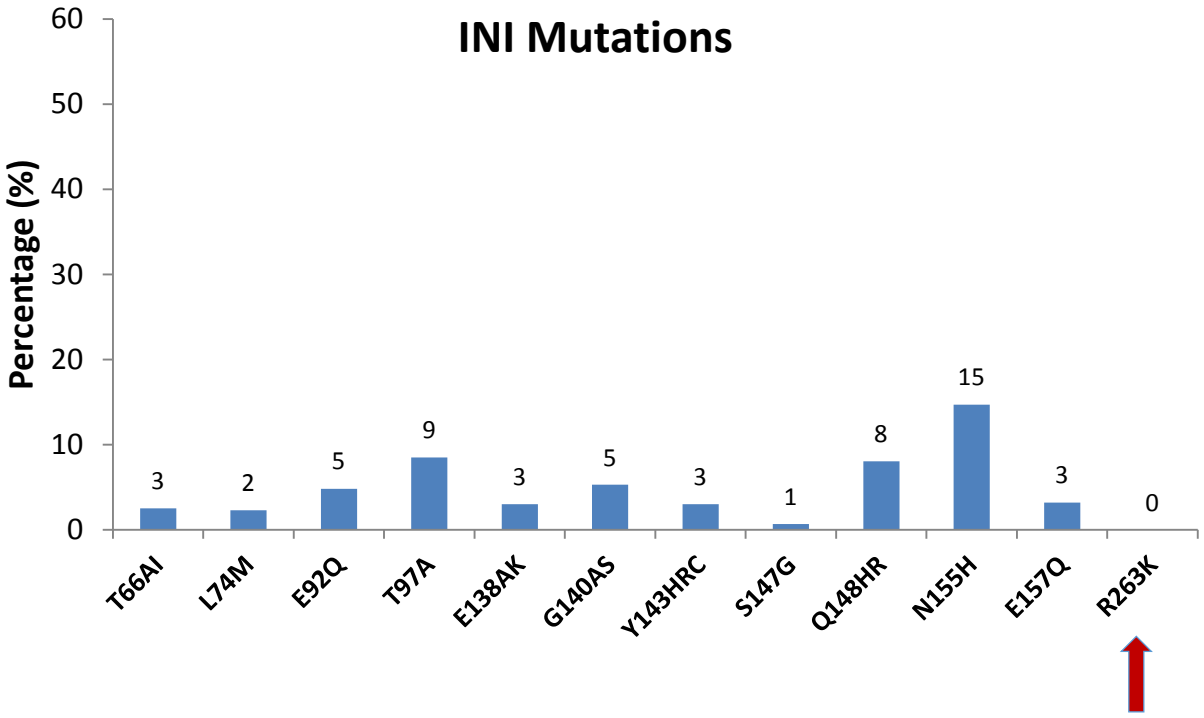


Resistance associated mutations at failure





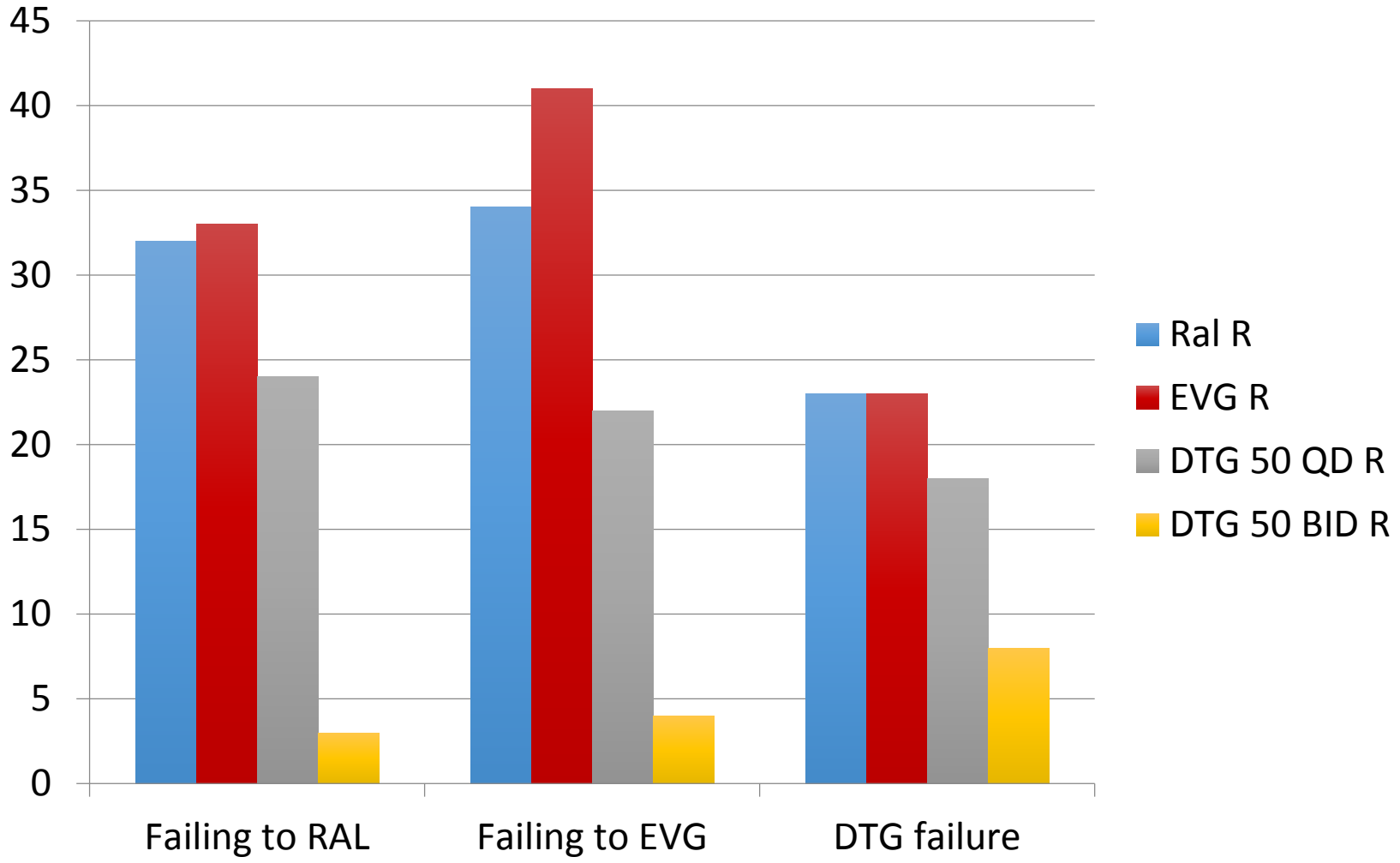
INI Resistance associated mutations at failure



- 64% of cases: no INIs resistance mutations

- 36% of cases: presence of INIs mutations
  - 22% of patients had 1 INIs resistance mutation
  - 8% of patients had 2 INIs resistance mutations
  - 6% of patients had >2 INIs resistance mutations

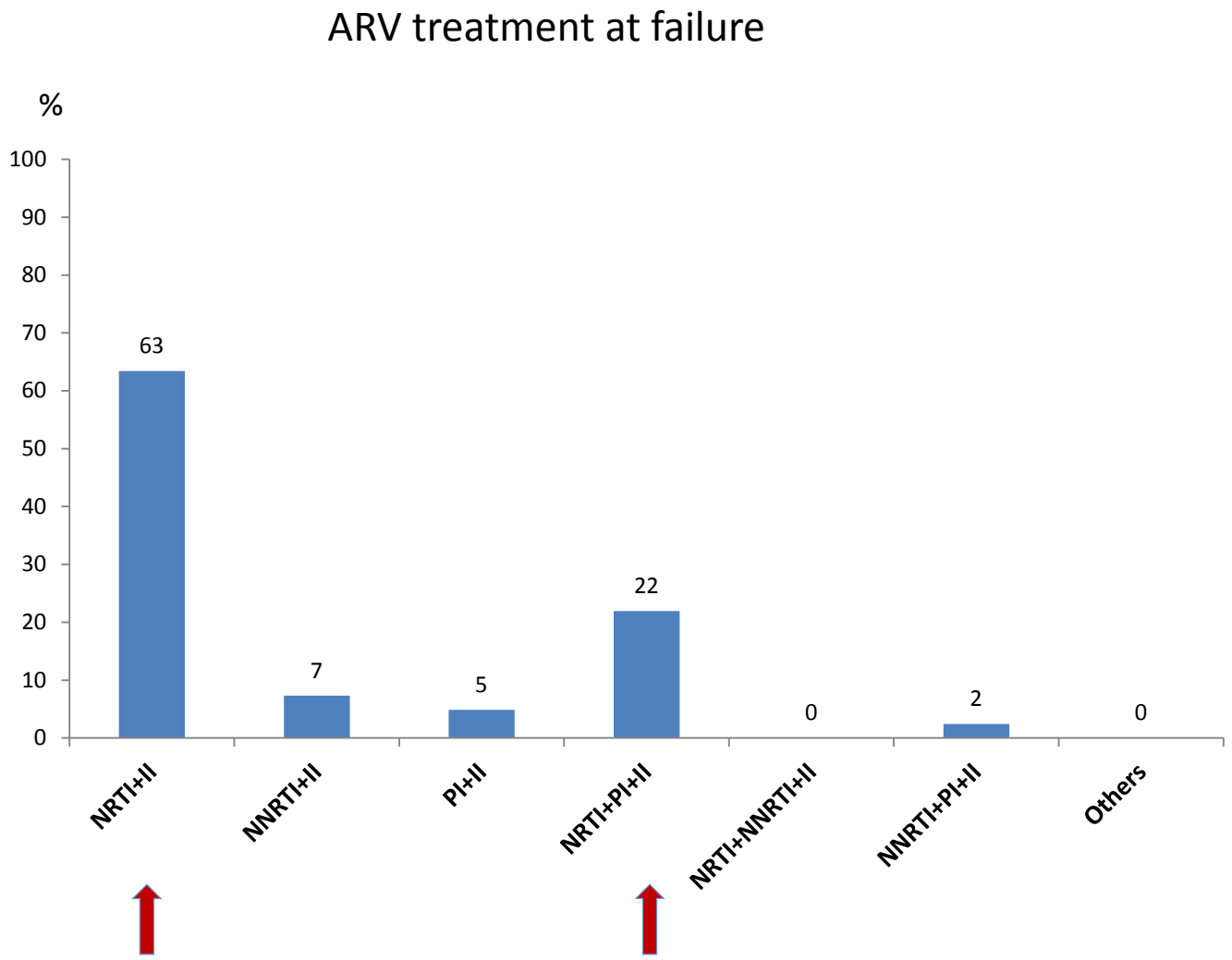
% of genotypic resistance to INIs at failure



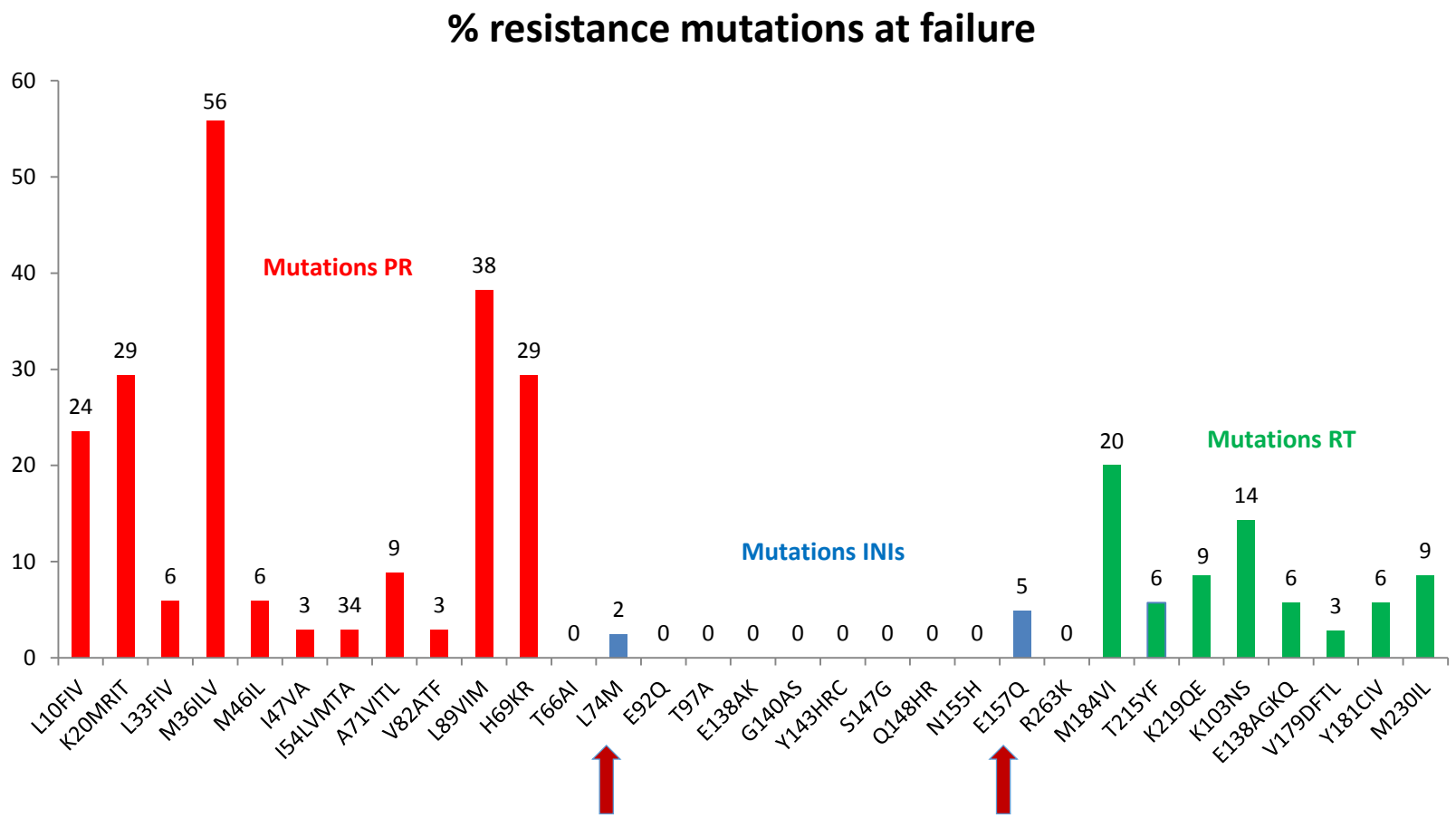
Patients treated by DTG as first INI (n = 41)

Variable	Median (IQR)
Age, years	47.7 [36.8 ; 54.0]
Time since HIV-1 diagnosis, years	10.7 [3.58 ; 22.4]
Duration of current INI regimen, years	0.4 [0.2 ; 0.7]
Nadir CD4 cell count, mm^3	110 [37; 254]
CD4 cell count at initiation, mm^3	320.5 [162 ; 640]
CD4 cell count at failure, mm^3	317.5 [173.5 ; 559.5]
viral load at initiation (Log_{10} cp/ml)	2.7 [2.0 ; 4.6]
viral load at failure (Log_{10} cp/ml)	2.7 [2.1 ; 4.4]
Sex, male (%)	24 (58)
HIV-1 subtype B	23 (56)

Patients treated by DTG as first INI (n = 41)



Patients treated by DTG as first INI (n = 41)



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Patients failing to DTG used as first INI (n = 41)

Resistance to INI	DTG_BID	DTG_QD	RAL	EVG
Susceptible (%)	39 (95%)	39 (95%)	41 (100%)	39 (95%)
Possible resistance (%)	2* (5%)	2* (5%)	NA	NA
Resistance (%)	0	0	0	2* (5%)

*2 patients with E157Q mutation alone

- Both B subtype
- In 1 case E157Q previously present before DTG use
- The other ?: Integrase baseline sequencing ongoing

E157Q is a polymorphism that is naturally present in 2.5% of cases (naive patients)
L74M is a polymorphism that is naturally present in 5% of cases (naive patients)

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Conclusions (1)

- Large cohort of patients (n = 431) failing INI-based regimens (RAL, EVG, DTG) followed in hospital clinical care
  - Inclusions are still ongoing until 31/12/17 (1500 Patients expected)

- Among patients failing an INI-based regimen, 36% harbored viruses with at least 1 INI resistance mutation
  - Close to 39% in 502 patients failing RAL-based regimen (Fourati et al. JAC 2015)
- RAM profiles: - N155H = 15%, T97A = 9% and Q148HR = 8%
  - Y143HRC and E138AK = 3%
  - No R263K

- Among patients failing to RAL, 32% harboured a virus resistant to RAL
- Among patients failing to EVG, 41% harboured a virus resistant to EVG
- High level of cross resistance between RAL and EVG

Conclusions (2)

- Among all patients failing to DTG (as the first INI or in patients previously exposed to RAL or EVG containing regimen)
  - 18% harboured a virus resistant to DTG QD and 8% to DTG BID.

- However, in patients failing to DTG when used as the first INI (INI naïve patients), no major resistance to INI was detected at failure.
  - Confirm resistance robustness of DTG

- Ongoing studies
  - Factors associated to the selection of INI resistance mutations
  - Plasma drug levels at failure (Dr Gilles Peytavin)
  - Ultradeep sequencing at failure

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