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Discordant predictions of residual activity could impact dolutegravir prescription upon raltegravir failure

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Background

- Treatment sequencing strategies expanded with the advent of integrase (IN) strand-transfer inhibitors (INSTIs).
- This drug class includes raltegravir (RAL), elvitegravir (EVG) and dolutegravir (DTG), all part of recommended first-line HIV-1 treatment
- DTG is a 2nd-generation INSTI with demonstrated activity against RAL-resistant isolates.
- The use of DTG in clinical practice should be informed by genotypic drug resistance testing.
- An extensive spectrum of INSTI resistance-association mutations (RAMs) has been identified, which can challenge clinical interpretation and affect optimization strategies

Objectives

- To determine the extent of disagreement in predicted residual DTG activity
- To identify mutational patterns for which uncertainty exists among HIV-1 expert systems

Methodology

- HIV-1 IN sequences from 216 RAL-treated patients from Belgium, Portugal and Stanford
- Rega subtyping tool V3.0 assigned subtype B in 72% of patients
- INSTI RAMs defined by their presence in IAS-USA list, expert drug-resistance interpretation systems and FDA/EMA INSTI package inserts
- Clinically informative resistance levels defined by HIVdb v7.0, ANRS v23 , Rega v9.1.0 and two categorization schemes (DTG-1, DTG-2) derived from information in the DTG package insert

Conclusions

- DTG may be potentially effective in the majority of HIV-1 patients failing a RAL-based regimen
- Consensus on interpreting the extent of residual activity is highly pathway-specific
- Uncertainty in clinical interpretation might affect individual patients management

Results
Prevalence of INSTI RAMs

- 43 of 79 pre-defined INSTI RAMs present in 188 (87%) of HIV-1 patients with RAL exposure
- Signature mutations: N155H (25.4%), Q148H (16.2%) and Y143R (8.3%)

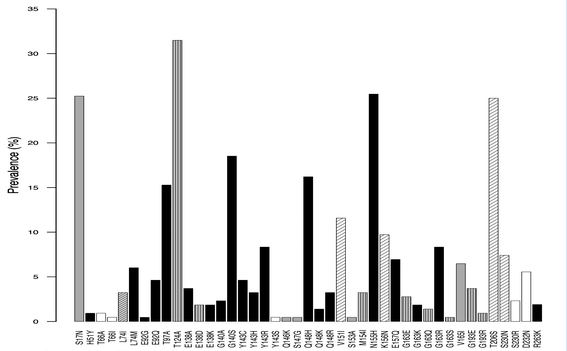


Figure 1: Genotypic INSTI resistance after raltegravir (RAL) exposure: Prevalence of INSTI resistance mutations, as defined in methodology section: ■ associated with raltegravir (RAL), elvitegravir (EVG) and dolutegravir (DTG) resistance, □ associated with RAL and EVG resistance, ▨ associated with EVG and DTG resistance, ▨ solely associated with RAL resistance, ▩ solely associated with EVG resistance and ▥ solely associated with DTG resistance.

Results
Predicted susceptibility levels

- High level of concordance in RAL activity between algorithms HIVdb, ANRS and Rega
- High level of discordance in predicted DTG activity between the three expert algorithms and two schemes from package inserts
- Concordant R/ IR DTG scored in 7.4% of patients, but individual systems scored IR/R more often, from 20.4% (DTG-2) to 31% (HIVdb and DTG-1)

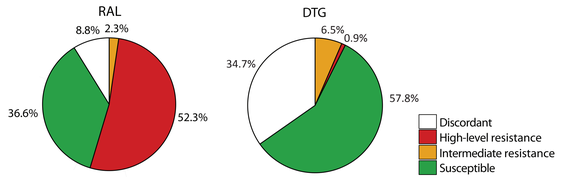
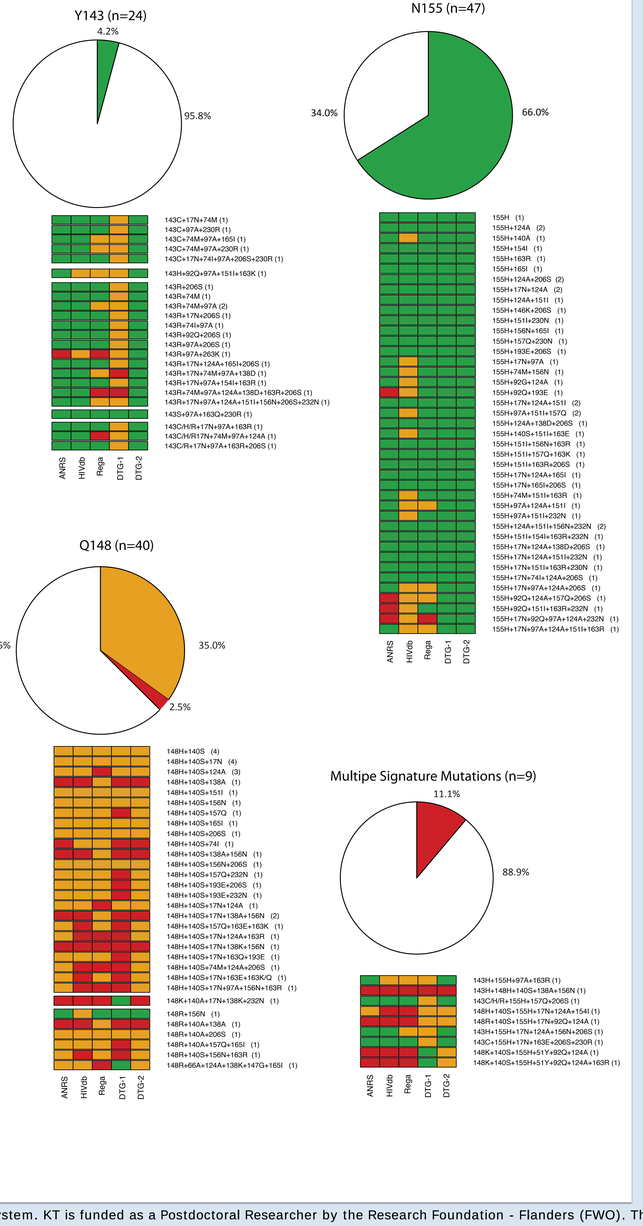


Figure 2: Frequency of concordant susceptible, intermediate resistant, resistant and discordant scores for RAL and DTG. For ANRS, only RAL resistance levels S and R were defined. **DTG-1**: poor virologic response was observed in VIKING-3 study patients displaying Q148HR and at least 2 mutations of L74IM, E138ADKT, G140AS, Y143HR, E157Q, G163EKQRS or G193ER, or in patients having at least 3 mutations of L74IM, E138ADKT, G140AS, Y143HR, Q148HR, E157Q, G163EKQRS or G193ER (respectively 18% and 25% of patients obtained <50 RNA copies/ml at w24), and therefore these patterns were categorized as **R**. A diminished response was observed in patients displaying Y143CHR without any Q148 mutation or displaying Q148HR and G140AS without any other INSTI mutation (<50 RNA copies/ml at w24 in 56% of patients), and these patterns were categorized as **IR**. All other mutational combinations were scored **S**. **DTG-2**: mutation patterns associated with reduced *in vivo* response rates were translated into **R** for any Q148 mutation and at least 2 mutations of L74I, E138AKT or G140ACS (25% of patients obtained <50 copies/ml at w24), into **IR** for any Q148 mutation and 1 mutation of L74I, E138AKT or G140ACS (65% of patients obtained <50 RNA copies/ml at w24) and into **S** for any other mutation combination mutations (Castagna et al, JID 2013).

Results
Individual mutation patterns and clinical interpretation for DTG

- A total of 141 INSTI mutational patterns classified into 6 'signature' groups
- Y143 group contained 23 patterns
  - Y143R (71%). Y143C (33%). Y143H (13%). Y143S (4%)
  - T97A (75%). T206S (38%). L74M (38%). T124 (17%)
  - S scored in 69% and R in 5% of all predictions
  - Concordant S score in 4% of patients
- Q148 group contained 31 patterns
  - Q148H (83%). Q148R (15%). Q148K (3%)
  - G140S (85%). K156N (23%). T124A (18%). T206S(13%)
  - S scored in 3%. IR in 68% and R in 29% of predictions
  - Concordant IR score in 35% and R score in 3% of patients
  - Predominantly (95%) observed in subtype B infected patients
- N155H group contained 41 patterns
  - T124A (47%). V151I (43%). T206S (23%). T97A (17%)
  - S scored in 89% of all predictions
  - Concordant S score in 66% of patients
- Multiple signature mutations in 9 patterns
  - S in 33%. IR in 31% and R scored in 36% of all predictions
  - Discordant score in 89% of patients
- No signature mutation in 37 patterns



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