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Poster #

Integrase Resistance Correlates of Response to Dolutegravir (DTG) through 48 Weeks

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Introduction

- The VIKING-3 (n=183)[1] and VIKING-4 (n=30)[2] (V 3/4) studies examined DTG 50mg twice-daily in patients with resistance to multiple ARV's, including integrase inhibitors (INI).
- Here we summarize previously derived baseline integrase (IN) genotypic and phenotypic correlates of Day 8 response from VIKING 3 and assess them using the larger V 3/4 combined population at Weeks 24 and 48.

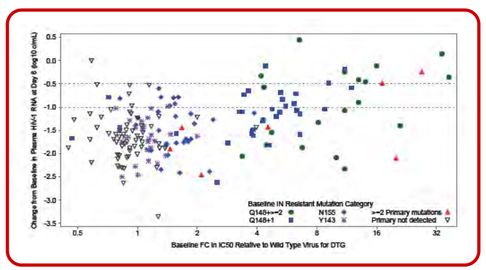
Methods

- Determine Baseline Correlates to Response at Day 8 using VIKING 3 Data [3]
  - Phenotypic Prediction of Response to DTG - by estimating DTG FC cut-offs that correspond to antiviral response; full (>1 $\log_{10}$),intermediate (0.5-1.0 $\log_{10}$), or no response (<0.5 $\log_{10}$) using non-linear logistic regression modelling
  - Genotypic prediction of response to DTG -
    - Prevalence of resistance-associated mutations and co-incidence of mutation pairs at Baseline were examined.
    - Genotypic correlates to responses were determined by multivariate logistic regression analyses
- Assess IN resistance correlates to long-term response using V 3/4 pooled data
  - DTG FC cutoffs (if can be determined) and-DTG FC groups proposed by FDA (<3, 3-<10, ≥10) for USPI were used to summarize Week 24/48 response.
  - Derived baseline IN mutation groups were used to summarize Week 24/48 responses.

Results

Baseline Correlates to Response at Day 8 using VIKING 3 Data

Figure 1. Baseline IN Resistance and Response at Day 8



- Overall, Day 8 change from baseline:-1.43 log10 copies/mL, *P*<0.001 [95%CI,-1.52 to -1.34] (ITT-E, N=183)
- No definite DTG FC cut-offs were identified due to limited numbers of non-responders and few viruses with high DTG FC.

Table 1. Prevalence of IN Mutations at Baseline

	DTG 50mg BID	
IN Resistance Mutation	All Subjects (N=183) n(%)	Q148 Virus (N=57) n(%)
Any IN Resistance Mutation	136 (74%)	57 (100%)
E92Q*	2 (1%)	0
T66A/I/K*	4 (2%)	2 (4%)
L68I/V	4 (2%)	0
G193E	6 (3%)	4 (7%)
S147G	5 (3%)	4 (7%)
Q95K	7 (4%)	0
E157Q	15 (8%)	2 (4%)
G163K/R	18 (10%)	2 (4%)
E138A/K/T	24 (13%)	20 (35%)
V151I	27 (15%)	3 (5%)
T97A	32 (17%)	1 (2%)
Y143C/H/R*	32 (17%)	2 (4%)
L74I/M	35 (19%)	7 (12%)
N155H*	36 (20%)	0
G140A/C/S	54 (30%)	53 (93%)
Q148H/K/R*	57 (31%)	57 (100%)

*Primary IN resistance mutation

Identification of IN Mutations Predicting Antiviral Response

- A pair-wise correlation beween pre-specified IN mutations confirmed high correlation of G140A/C/S and Q148H/K/R (p<0.001).
- Univariate testing of each baseline IN mutation on Day 8 responses identified E138A/K/T, E157Q, E92Q, G193E, L68I, L74I, S147G, T97A, Y143H, G140A/C/S and Q148H/K/R as having a moderate impact (p<0.3) and were retained for further analysis.
- IN mutations occurring in ≥70% of models from 3000 Bootstrap re-sampling analyses were **E138A/K/T, E92Q, L68I, L74I, G140A/C/S and Q148H/K/R**

Results, cont.

Table 2. Results of Multivariate Model for Deriving IN Mutation Groups

Effect	Estimate	SE	P Value
Q148H/K/R**	0.47	0.094	<0.001
L74I	0.27	0.131	0.037
E138/AK/T	0.25	0.130	0.052
L68I	0.58	0.372	0.118
E92Q	-0.58	0.380	0.129

** G140A/C/S is highly correlated with Q148H/K/R

- L68I and E92Q remained in the final model but their estimates were subject to large variation due to a small number of virus with these mutations.

Final Derived IN Mutation Groups

- **No Q148:** No presence of Q148H/K/R
- **Q148+1 :** Q148H/K/R with one mutation (G140A/C/S, L74I, E138A/K/T)
- **Q148 +≥2**: with two or three mutations (G140A/C/S, L74I, E138A/K/T)

IN Resistance Correlates to Long-term Response Using V 3/4 Pooled Data

Table 3. Response by Baseline DTG FC at Week 24 and 48

DTG 50 mg BID (ITT-E, Snapshot algorithm)			
DTG FC Group		Week 24 <50 c/mL	Week 48 <50 c/mL
	N*	N(%)	N(%)
All	213	140 (66%)	128 (60%)
<3	138	104 (75%)	94 (68%)
3 to <10	47	23 (49%)	21 (45%)
≥10	20	5 (25%)	5 (25%)

*Note: 8/213 have missing DTG FC at Baseline

Table 4. Response by Derived IN Mutation Groups at Week 24 and 48

DTG 50 mg BID (ITT-E, Snapshot algorithm)			
Baseline IN Mutation Group		Week 24 <50 c/mL	Week 48 <50 c/mL
	N	N(%)	N(%)
All	213	140 (66%)	128 (60%)
No Q148	140	109 (78%)	98 (70%)
Q148 +1*	48	25 (52%)	23 (48%)
Q148 +≥2*	25	6 (24%)	7 (28%)

*L74I, E138A/K/T, G140A/C/S

Discussion

- The DTG FC groups <3, 3-<10, ≥10 (as proposed by the FDA for the USPI) distinguished long-term response rates at Week 24 and 48 in a similar fashion to that of the derived IN mutation groups, however these groups do not represent distinct clinical cut offs for DTG.
- The derived IN mutation groups, No Q148, Q148+1 and Q148 +≥2 were effective in differentiating Week 24 and Week 48 responses. This analysis identified specific key secondary IN mutations, L74I, E138A/K/T, and G140A/C/S impacting response when associated with the Q148H/K/R;
  - Possible additional IN mutations may be added to this list from an examination of larger epidemiological cohorts.[4] For example, L74M was detected in only 3 subjects harboring Q148H/K/R virus in this study, but it would be postulated it's impact would be similar to that of L74I.
- In the univariate testing of each baseline IN mutation, 5 additional IN mutations with potential impact on response were identified; E157Q, G193E, S147G, T97A, and Y143H. However, multivariate regression analyses did not retain these substitutions.
- The analysis for deriving baseline predictors of response was performed at Day 8 (functional DTG monotherapy) to limit confounders of response. Later timepoint (Weeks 24 /48), analyses may result in less accurate correlates of response due to difficulty in accurately controlling for other confounders of response such as adherence to treatment and the activity of the background ART especially in this highly treatment experienced population.
- Similar analyses of antiviral response by baseline integrase resistance in larger cohorts of patients receiving DTG 50 mg BID regimen will be valuable to validate and/or further refine the IN genotypic groups and definite DTG cut-off's in predicting response to DTG.

Conclusions

- Three derived baseline IN genotypic groups (No Q148 mutations, Q148 +1, and Q148 +≥2) were good predictors for DTG responses through Week 48, and thus provide guidance for the clinical use of DTG in patients with INI-resistant virus.
- Response rates were maintained between Week 24 and 48 for all IN genotypic groups.

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  Castellino S, Moss L, Wagner D, et al. Metabolism, excretion, and mass balance of the HIV-1 integrase inhibitor dolutegravir in humans. *Antimicrob Agents Chemother*. 2013;57(8):3536-3546.

  Walmsley S, Antela A, Clumeck N, et al. Dolutegravir (DTG; S/GSK1349572) plus abacavir/lamivudine once daily statistically superior to tenofovir/emtricitabine/efavirenz: 48-week results from SINGLE (ING114467). Abstract H-556b. Presented at: 52nd Interscience Conference on Antimicrobial Agents and Chemotherapy; September 9-12, 2012; San Francisco, CA.