Resistance Post Week 48 in ART-Experienced, Integrase Inhibitor-Naïve Subjects with Dolutegravir (DTG) vs. Raltegravir (RAL) in SAILING (ING111762)

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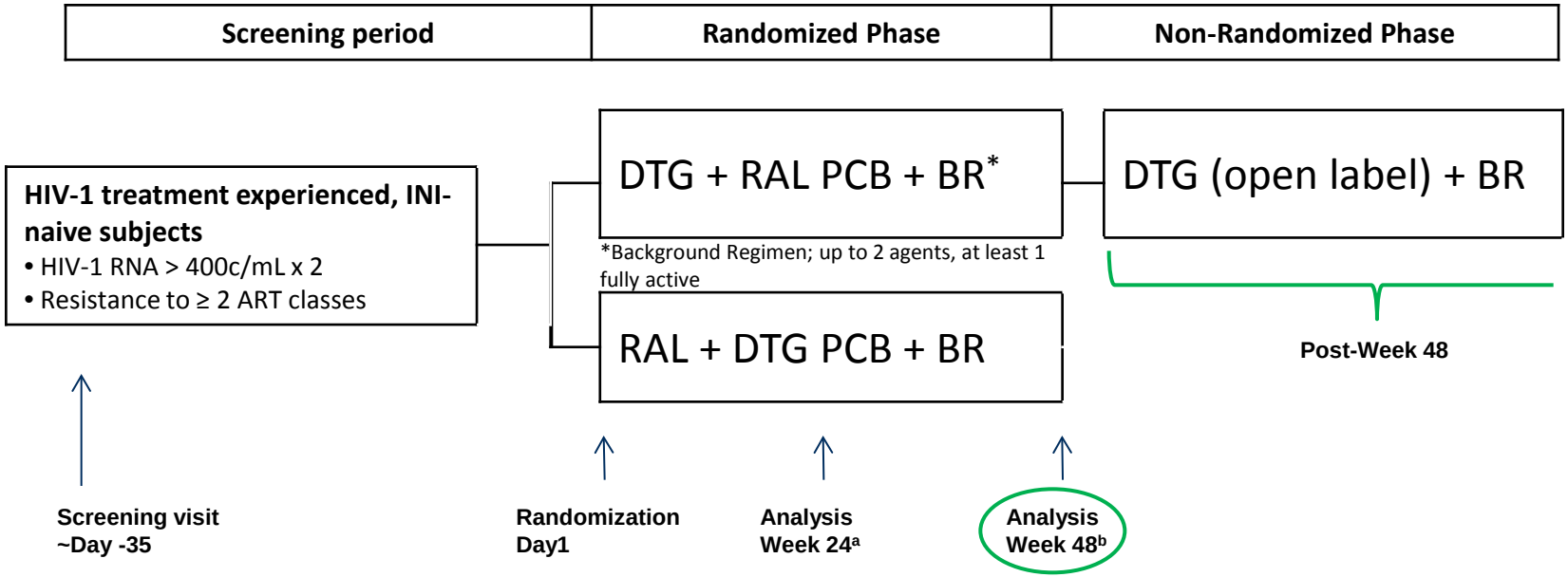
13th European HIV & Hepatitis Workshop; June 3-5, 2015; Barcelona, Spain

Study Design



Week 48 Results

- Dolutegravir 50 mg once daily was superior to raltegravir 400 mg twice daily: 251 (71%) with HIV-1 RNA<50 c/mL versus 230 (64%); (adjusted difference 7·4%, 95% CI 0·7 to 14·2; p=0·03).
- Fewer subjects failed with INI-genotypic or -phenotypic resistance on DTG (4/354, 1%) versus RAL (17/361, 5%), p=0.003.

a Underwood, et al. Abs#21. IDRW June 4-8, 2013. Toronto, Canada
b Cahn, et al. Lancet 2013; 382: 700–08

SAILING Resistance Through Week 48

- Emergent IN substitutions for two subjects on DTG at R263K or V260I/R263K conferred <2 fold change (FC) in IC_{50} for DTG and RAL[a,b]
- Subjects had fluctuating viral load or DTG level measured below the quantitation limit[b]
  - Evidence for non-optimal adherence leading to PDVF and emerging resistance

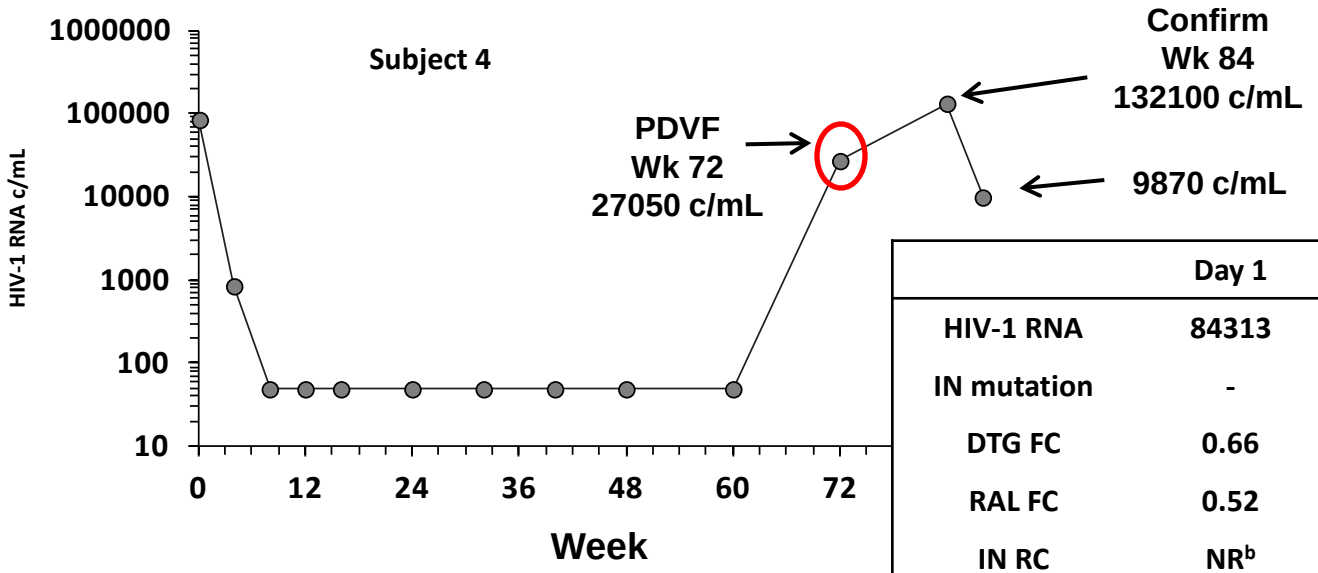
a Cahn, et al. Lancet 2013; 382: 700–08
b Underwood, et al. Abs#21. IDRW June 4-8, 2013. Toronto, Canada

SAILING Post Week 48 Endpoint

- Subjects could continue to receive DTG until:
  - locally approved and available
  - clinical benefit is lost
  - protocol-defined reason for discontinuation
  - clinical development of the compound is terminated
- Of subjects remaining on DTG three have met PDVF and harbored emergent INI resistance

Subject 4: Virologic Characteristics

- Day 1: Clade C; PSS = 2, GSS = 2
- Regimen ($PSS_{Day\ 1}$): tenofovir (1) and darunavir/r (1)
- DTG C0[a]: Wk 4 = 1.78 µg/mL, Wk 24 = not evaluable, Wk 48 = 1.23 µg/mL



	Day 1	PDVF
HIV-1 RNA	84313	27050
IN mutation	-	I60L, T97A, N155H
DTG FC	0.66	2.4
RAL FC	0.52	113
IN RC	NR[b]	NR

PDVF BR: No emergent resistance, loss of RT M184V and PI L10F, M36I, M46I, I54V, V82A.

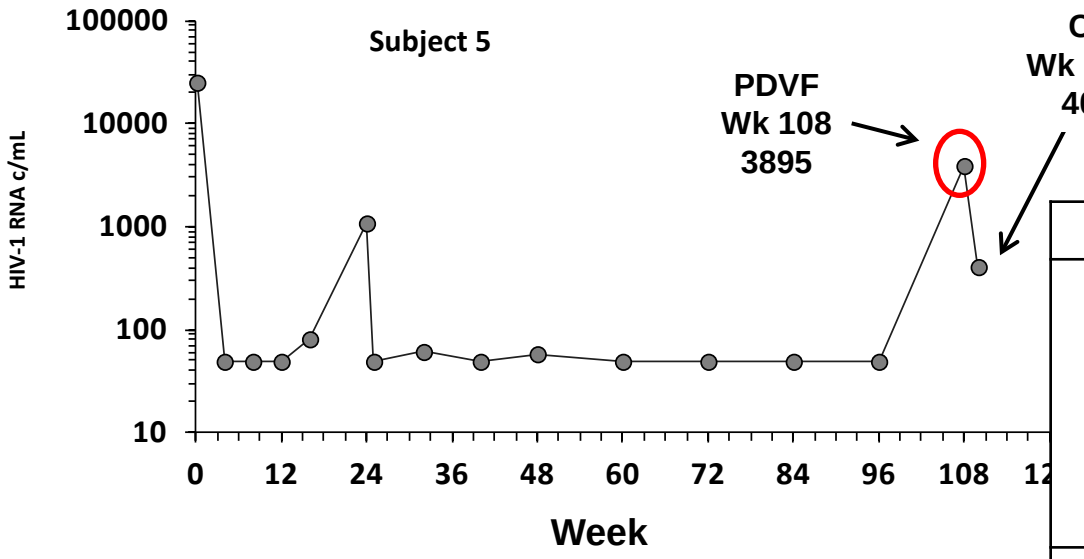
- **Non-adherent with investigational product (IP)(protocol deviation)**
- DTG FC in line with prior RAL selected N155H pathway isolates[c]

[a] Geometric Mean Week 4 + Week 24 C0 0.86 µg/mL (CVb=140%)
[b] Could not be determined
* Wildtype RC = 100%

c Underwood, et al. Abs#85. IDRW June 4-8, 2013. Toronto, Canada

Subject 5: Virologic Characteristics

- Day 1: Clade A; PSS = 2, GSS = 0.5
- Regimen ($PSS_{Day\ 1}$): abacavir (1) and lamivudine (1)
- DTG C0[a]: Wk 4 = 1.14 µg/mL; **Wk 24 = <0.02 µg/mL (BQL)**; Wk 48 = 1.60 µg/mL



	Day 1	PDVF
HIV-1 RNA	25105	3895
IN mutation	-	N155H
DTG FC	0.97	1.8
RAL FC	1.18	12
IN RC	NR[b]	NR

PDVF BR: No emergent resistance, loss of M184M/V

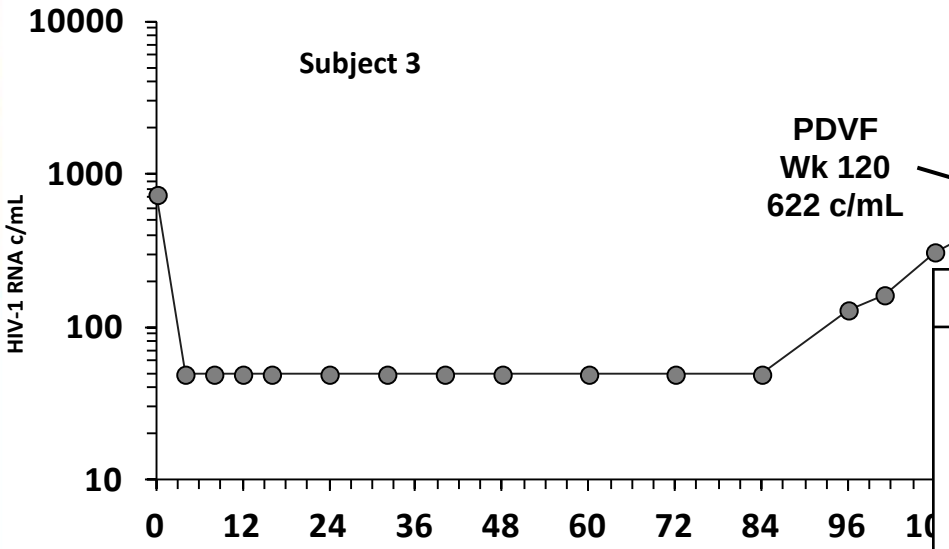
- **DTG trough below limit of detection Week 24**
- DTG FC in line with prior RAL selected N155H pathway isolates[a]

[a] Underwood, et al. Abs#85. IDRW June 4-8, 2013. Toronto, Canada

[a] Geometric Mean Week 4 + Week 24 C0 0.86 µg/mL (CVb=140%)
[b] Could not be determined
* Wildtype RC = 100%

Subject 3: Virologic Characteristics

- Day 1: Clade B; PSS = 2, GSS = 2
- Regimen ($PSS_{Day\ 1}$): tenofovir (1) and emtricitabine (1)
- DTG C0[a]: Wk 4 = 0.36 µg/mL, Wk 24 = 0.22 ug/mL, **Wk 48 = 0.03 ug/mL**



	Day 1	PDVF	Confirm.
HIV-1 RNA	733	622	1054
IN mutation	-	A49G, S230R, R263K	A49G, S230R, R263K
DTG FC	0.73	3.82	5.77
RAL FC	0.54	2.39	2.62
IN RC*	20%	7.1%	12%

PDVF BR: No emergent resistance, and no NRTI resistance at any time points

- In addition to R263K both A49G and S230R were observed at Week 120 and Week 132
- Decreased replication capacity with A49G,S230R,R263K substitutions

[a] Geometric Mean Week 4 + Week 24 C0 0.86 µg/mL (CVb=140%)
[b] Could not be determined
* Wildtype RC = 100%

Subject 3: Clonal analysis

		IN Genotype		FC IC50 vs WT			
Time	**Source**	**n[a]**	**Sequence**	**n[a]**	**DTG**	**EVG[b]**	**RAL**
Day 1	Pop	-	wt	-	0.73	-	0.54
	Clone	8	wt	4	0.87	1.10	0.75
Wk 120	Pop	-	A49G, S230R, R263K	-	3.82	-	2.39
	Clone	8	A49G, S230R, R263K	4	5.80	7.65	2.67
Wk 132	Pop	-	A49G, S230R, R263K	-	5.77	-	2.62
	Clone	4	A49G, S230G[c], R263K	2	4.07	3.77	1.71
	Clone	4	A49G, S230R, R263K	2	5.66	8.13	2.80

a. Clone data available, median is calculated if n>1; b. EVG data not available for population testing; c. S230 to S230R and S230R to S230G substitutions required two independent single nucleotide changes.

- DTG FC data for Week 120 clones was slightly higher than the population data (potential mixture effect?); EVG least susceptible.
- Week 132 clones showed S230**G** present with A49G and R263K, though it was not present by population sequence.
- The S230**G** substitution showed less effect on FCs than S230**R**.

Summary

- Low or BQL DTG levels at some timepoints, or stated non-compliance with IP, suggests that non-adherence likely contributed to PDVF and emergent INI resistence for the subjects described.
- N155H pathway isolates on DTG were similar to N155H pathway virus observed during RAL therapy.
- R263K IN pathway virus FCs at Week 120 and at Week 132 for DTG were slightly higher than prior analyses from two PDVF subjects with R263K (with DTG FCs < 2) through Week 48[a,b].
- DTG FC and minority species codon changes for Subject 3 were consistent with evolving resistance in the context of R263K during continued DTG therapy.
- Additional clinical data is needed to better assess DTG resistance.

a Cahn, et al. Lancet 2013; 382: 700–08
b Underwood, et al. Abs#21. IDRW June 4-8, 2013. Toronto, Canada

Acknowledgements

We would like to thank subjects and their supporters, study investigators and site staff, and contributors from GSK and ViiV Healthcare.