ARCHIVED RESISTANCE AND RESPONSE TO <40 C/ML AND TND – DTG/3TC FDC AT WEEK 48 IN SALSA

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Introduction

- The SALSA study showed switching to DTG/3TC FDC was non-inferior to continuing current antiretroviral regimen (CAR) at Week 48,[1] with 94% (232/246) vs 93% (229/247) having HIV-1 RNA viral load (VL) <50 c/mL by FDA Snapshot algorithm.
- The clinical implications of genotypic resistance mutations in archived proviral DNA need to be better understood, as proviral resistance is sometimes used where plasma levels of HIV-1 are below standard resistance testing levels.
- The impact of archived baseline (BL) resistance with 2-drug regimens has been assessed, including for the M184V mutation[2-4]; additional assessments are needed to compare potential impact across more patient populations.
- This post-hoc analysis assesses proportion of BL participant samples with archived resistance and virologic response through 48 weeks using the stringent VL measure <40 c/mL and target not detected (TND).

Methods

- Adults with VL <50 c/mL for ≥6 months without evidence of virologic failure were randomized to DTG/3TC FDC or continued CAR. Historic genotypic resistance results were submitted if available, and participants were excluded if IAS-USA 2019 DTG-associated or major NRTI resistance was present.
- RealTime HIV-1 assay provided quantitative VL from 40 to 10,000,000 c/mL, and qualitative target detected (TD) or TND data for VL <40 c/mL. BL proviral genotyping used Monogram Biosciences GenoSure Archive assay (15% cutoff for mutation prevalence).
- Virologic outcomes were determined using the FDA Snapshot algorithm at Week 48 using the last on-treatment HIV-1 RNA VL. The proportion of participants with HIV-1 RNA thresholds at <50 c/mL and ≥50 c/mL, as well as using the HIV-1 RNA <40 c/mL and TND threshold, were assessed by treatment arm, at overall across arms level, by BL mutation, and by BL resistance class.
- The primary population assessed here was the PRAP (proviral resistance analysis population). PRAP is defined as all participants in the intention-to-treat–exposed (ITT-E) population, having BL proviral genotype data, at least one post-BL on-treatment VL result, and not meeting protocol deviation criteria.
- The list of major RAMs used in these analyses was based on the IAS 2019 update. The pre-specified INSTI substitutions list used (with major IAS INSTI mutations bolded) is: H51Y, **T66I**/A/K, L68I/V, L74M/I, **E92Q**/V/G, Q95K, T97A, **G118R**, **F121Y**, E138A/K/D/T, G140A/C/R/S, **Y143C/H/R**/K/S/G/A, P145S, Q146P, **S147G**, **Q148H**/K/R, V151I/L/A, S153F/Y, **N155H**/S/T, E157Q, G163R/K, G193E, S230R, **R263K**.

Results

- Of 246 and 247 participants randomized to the DTG/3TC and CAR arms, respectively, BL proviral DNA genotypes were generated for 196/224 and 189/216 available samples. Of these with BL genotypes, 192/196 and 185/189 fit PRAP criteria, with 4 per arm excluded as protocol deviations.
- Time from first ART to study start for the PRAP was, respectively, [median (range)] 66.1 (4,240) and 74.4 (12,253) months for the DTG/3TC and CAR arms.

Using a stringent VL measure of <40 c/mL and TND, responses for DTG/3TC 2-drug regimen vs CAR 3-drug regimen were similar, including those with archived M184V/I, which was present in 3% of each arm at BL.

Table 1. Mutation Frequencies Were Broadly Similar Across Arms, Though With Generally Small Ns for Non-polymorphic Positions

Class	Mutation[a]	DTG/3TC N (%)	CAR N (%)	Total N (%)
Major NRTI		**15[b] (8%)**	**16 (9%)**	**31 (8%)**
	Any TAM[c]	7 (4%)	5 (3%)	12 (3%)
	A62V	5 (3%)	4 (2%)	9 (2%)
	K70E	0	1 (<1%)	1 (<1%)
	L74V	0	1 (<1%)	1 (<1%)
	M184I	0	1 (<1%)	1 (<1%)
	M184V	5 (3%)	4 (2%)	9 (2%)
Major NNRTI		**28 (15%)**	**17 (9%)**	**45 (12%)**
	E138A	6 (3%)	6 (3%)	12 (3%)
	E138G	2 (1%)	1 (<1%)	3 (<1%)
	E138K	1 (<1%)	2 (1%)	3 (<1%)
	E138R	1 (<1%)	0	1 (<1%)
	G190A	1 (<1%)	2 (1%)	3 (<1%)
	H221Y	1 (<1%)	0	1 (<1%)
	K101E	2 (1%)	0	2 (<1%)
	K103N	9 (5%)	2 (1%)	11 (3%)
	K103S	0	1 (<1%)	1 (<1%)
	M230I	0	1 (<1%)	1 (<1%)
	P225H	1 (<1%)	0	1 (<1%)
	V106A	1 (<1%)	1 (<1%)	2 (<1%)
	V108I	4 (2%)	1 (<1%)	5 (1%)
	Y181C	1 (<1%)	1 (<1%)	2 (<1%)
	Y188H	1 (<1%)	0	1 (<1%)
Major PI		**14 (7%)**	**12 (6%)**	**26 (7%)**
	D30N	1 (<1%)	5 (3%)	6 (2%)
	I54L	1 (<1%)	0	1 (<1%)
	I84V	0	1 (<1%)	1 (<1%)
	L90M	3 (2%)	0	3 (<1%)
	M46I	5 (3%)	5 (3%)	10 (3%)
Class	**Mutation**	**DTG/3TC N (%)**	**CAR N (%)**	**Total N (%)**
Major PI	(cont)			
	M46L	2 (1%)	0	2 (<1%)
	N88S	0	1 (<1%)	1 (<1%)
	Q58E	1 (<1%)	3 (2%)	4 (1%)
	V82A	1 (<1%)	0	1 (<1%)
Major INSTI		**1 (<1%)**	**4 (2%)**	**5 (1%)**
	Q148R	0	1 (<1%)	1 (<1%)
	Y143C	0	1 (<1%)	1 (<1%)
	Y143H	1 (<1%)	2 (1%)	3 (<1%)
Minor INSTI		**8 (4%)**	**5 (3%)**	**13 (3%)**
	E138K	2 (1%)	0	2 (<1%)
	E92G	1 (<1%)	0	1 (<1%)
	L74M	1 (<1%)	0	1 (<1%)
	S153F	1 (<1%)	0	1 (<1%)
	T97A	3 (2%)	5 (3%)	8 (2%)
Other INSTI[d]		**59 (31%)**	**54 (29%)**	**113 (30%)**
	E138D	0	1 (<1%)	1 (<1%)
	E157Q	4 (2%)	8 (4%)	12 (3%)
	G163K	0	2 (1%)	2 (<1%)
	G163R	1 (<1%)	0	1 (<1%)
	G193E	25 (13%)	17 (9%)	42 (11%)
	H51Y	0	1 (<1%)	1 (<1%)
	L68I	1 (<1%)	0	1 (<1%)
	L68V	1 (<1%)	1 (<1%)	2 (<1%)
	L74I	20 (10%)	20 (11%)	40 (11%)
	P145S	1 (<1%)	0	1 (<1%)
	Q95K	0	2 (1%)	2 (<1%)
	S230R	1 (<1%)	0	1 (<1%)
	V151I	6 (3%)	4 (2%)	10 (3%)

Table is based on the PRAP (proviral resistance analysis population) as described in the Methods section. [a]A participant can have more than one mutation including across different classes. [b]Numerator is the number of participants with a particular mutation or mutation mixture with wild-type detected. Denominators are those with BL proviral genotype generated. [c]TAMs: thymidine analogue mutations including M41L, D67N, K70R, L210W, T215F/Y, and K219E/Q. [d]Other INSTIs are pre-specified substitutions that are neither IAS major nor minor.

- Frequency of any overall major class resistance was similar across treatment arms with 54/192 (28%) receiving DTG/3TC vs 40/185 (22%) receiving CAR.
- M184V/I was similarly distributed with 3% frequency across both the DTG/3TC (5 M184V) and CAR (4 M184V and 1 M184I) arms.
  - M184V/I was present with ≥1 major resistance mutation for DTG/3TC in 2 participants and for CAR in 3 participants.

Table 2. VL <40 c/mL and TND Proportions at Week 48, Overall and by Key and Most Frequent Baseline Resistance, Were Similar Across Arms, Including M184V/I

Mutation[a]	DTG/3TC (N=192)		CAR (N=185)		Mutation	DTG/3TC (N=192)		CAR (N=185)	
Category	**n (%)[b]**	**TND (%)[c]**	**n (%)**	**TND (%)**	**Category**	**n (%)**	**TND (%)**	**n (%)**	**TND (%)**
NRTI Total[d]	15 (8%)	13 (87%)	16 (9%)	11 (69%)	INSTI Major Total[d]	1 (<1%)	1 (100%)	4 (2%)	4 (100%)
Any TAM[e]	7 (4%)	6 (86%)	5 (3%)	4 (80%)	Y143H	1 (<1%)	1 (100%)	2 (1%)	2 (100%)
A62V	5 (3%)	4 (80%)	4 (2%)	3 (75%)	Q148R	0	NA	1 (<1%)	1 (100%)
M184V	5 (3%)	4 (80%)	4 (2%)	2 (50%)	Y143C	0	NA	1 (<1%)	1 (100%)
M184I	0	NA	1 (<1%)	1 (100%)	INSTI Minor Total[d]	8 (4%)	8 (100%)	5 (3%)	4 (80%)
NNRTI Total[f]	28 (15%)	21 (75%)	17 (9%)	13 (77%)	T97A	3 (2%)	3 (100%)	5 (3%)	4 (80%)
PI Total[f]	14 (7%)	13 (93%)	12 (6%)	9 (75%)	E138K	2 (1%)	2 (100%)	0	NA

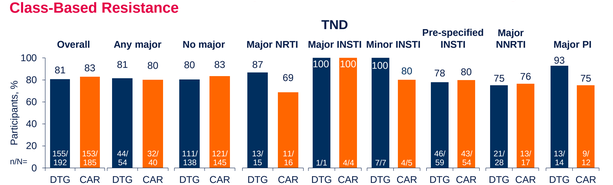
Table is based on the PRAP (see Methods section). NA, not applicable. [a]A participant can have more than one mutation including across different classes. [b]For n (%) of total, numerator is the number of participants with a particular mutation or mutation mixture with wild-type detected, and denominators are those with BL proviral genotype generated. [c]For TND (%), numerators are the number of samples in the category with TND, and denominators are the number of participants in that category with a particular mutation or mutation mixture with wild-type detected. [d]NRTI totals count participants with at least one major NRTI mutation, including in the TAMs subgroup. NRTI mutations with overall across arm frequency <1% are not in the table, except for key M184I; thus, K70E and L74V data are provided in footnote below. [e]TAMs: thymidine analogue mutations including M41L, D67N, K70R, L210W, T215F/Y, and K219E/Q. TAM totals contain at least one TAM mutation. [f]All INSTI major, and the minor INSTI mutations T97A and E138K, are included, but only totals are included for NNRTI and PI IAS major resistance in this table. Details for data not in Table 2 for NNRTI and PI, and less common NRTI and INSTI mutations, are presented below using data format: *"**Class Mutation** (DTG/3TC <40 c/mL, TND N/total mutation N, CAR <40 c/mL, TND N/total mutation N)"*: ***Major NRTI:*** *K70E (0/0, 0/1), L74V (0/0, 1/1).* ***Major NNRTI:*** *E138A (5/6, 5/6), E138G (1/2, 1/1), E138K (1/1, 2/2), E138R (1/1, 0/0), G190A (1/1, 2/2), H221Y (1/1, 0/0), K101E (1/2, 0/0), K103N (7/9, 1/2), K103S (0/0, 0/1), M230I (0/0, 1/1), P225H (0/1, 0/0), V106A (1/1, 0/1), V108I (3/4, 0/1), Y181C (0/1, 1/1), Y188H (1/1, 0/0).* ***Major PI:*** *D30N (1/1, 5/5), I54L (1/1, 0/0), I84V (0/0, 1/1), L90M (3/3, 0/0), M46I (5/5, 4/5), M46L (1/2, 0/0), N88S (0/0, 1/1), Q58E (1/1, 1/3), V82A (1/1, 0/0).* ***Minor INSTI:*** *E92G (1/1, 0/0), L74M (1/1, 0/0), S153F (1/1, 0/0).* ***INSTI pre-specified not in Table:*** *E138D (0/0, 1/1), E138K (2/2, 0/0), E157Q (3/4, 8/8), E92G (1/1, 0/0), G163K (0/0, 2/2), G163R (0/1, 0/0), G193E (16/25, 13/17), H51Y (0/0, 1/1), L68I (1/1, 0/0), L68V (1/1, 1/1), L74I (16/20, 14/20), L74M (1/1, 0/0), P145S (1/1, 0/0), Q148R (0/0, 1/1), Q95K (0/0, 1/2), S153F (1/1, 0/0), S230R (0/1, 0/0), T97A (3/3, 4/5), V151I (6/6, 4/4), Y143C (0/0, 1/1), Y143H (1/1, 2/2).*

- For M184V/I in the DTG/3TC and CAR arms, respectively, 4/5 vs 3/5 had VL <40 c/mL and TND.
- In the respective DTG/3TC and CAR arms, VL <40 c/mL and TND was observed for 1/1 and 4/4 in those with major INSTI mutations, and for 8/8 and 4/5 in those with minor INSTI mutations.

Discussion

- Proportions of TND were high and similar across the DTG/3TC and CAR arms, whether assessed by BL resistance mutations or by BL class resistance categories. The overall TND frequency is consistent with previously reported data for suppressed switch studies,[2] and for ART-naive studies[5] once HIV-1 RNA had suppressed.
- The clinical implications for very-low-level viremia measures remain exploratory, and resistance testing of archived proviral DNA should be used with caution.[6] Further related work may help inform HIV-1 clinical management use for these measures.

Figure 1. VL <40 c/mL and TND Proportions Were Similar Across Arms by Baseline Class-Based Resistance



Assessed using PRAP: proviral resistance analysis population is described in the Methods section. Proportions of TND used as numerator occurrences of TND, with denominator being the N occurrences of the associated BL resistance category.

- Overall proportions with TND at last available on-treatment VL in the DTG/3TC and CAR arms were 155/192 (81%) and 153/185 (83%), respectively, and similar across all categories in both arms.
  - Overall proportions using <50 c/mL (instead of <40 c/mL and TND) at last available on-treatment VL were, respectively, 191/192 (>99%) and 182/185 (98%) in the DTG/3TC and CAR arms.
- No participants in either arm met CVW criteria.

Conclusions

- In SALSA, DTG/3TC demonstrated non-inferior efficacy compared with CAR over 48 weeks. No participants in either arm met CVW.
- Using a more stringent measure of VL <40 c/mL and TND, responses for DTG/3TC vs CAR were similar including in those with BL archived M184V/I, which was present in 3% of each arm at BL.
- These data, as well as prior reported responses (HIV-1 RNA <50 c/mL) for DTG/3TC vs CAR (SALSA) or TAF-based regimen (TANGO), are supportive of the efficacy and potency of DTG/3TC in suppressed switch participants.

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