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ADVANCE TRIAL: HIGHER RISK OF TREATMENT-EMERGENT RESISTANCE ON FIRST-LINE TDF/FTC/EFV

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BACKGROUND

ADVANCE is an ongoing trial designed to evaluate dolutegravir (DTG) and tenofovir alafenamide fumarate (TAF) as candidates for first-line HIV treatment in South Africa. Participants were randomized over 96-weeks to three arms: TAF/FTC+DTG, TDF/FTC+DTG, and TDF/FTC/EFV (n=1053). Non-inferior efficacy of the two DTG arms compared to standard of care was established at the primary endpoint (Week 48).

The aim of this analysis was to evaluate rates of drug resistance in ADVANCE participants experiencing virological failure.

METHODS

Virological failure (VF) was defined as any of the following:
- ≥1000 copies/mL after 12 weeks of randomization
- ≥200 copies/mL after 24 weeks of randomization
- ≥50 copies/mL after 48 weeks of randomization

Protocol-defined VF (PDVF) was defined as:
- 2x ≥1000 copies/mL after 12 weeks of randomization

Participants with an HIV RNA result ≥1000 copies/mL after 12 weeks were genotyped, together with a test of their stored baseline sample.

The number of genotyped patients with VF and treatment-emergent major NRTI or NNRTI mutations was compared between arms (Fisher's exact). Mutations were defined using the Stanford University HIV Drug Resistance Database.

For individuals with VF, the following three HIV RNA readings were assessed to observe viral patterns and evaluate the proportion of individuals that were re-suppressed to HIV RNA <50 copies/mL by visit three (last observation carried forward if individual censored; LOCF).

RESULTS

- In total 177/1,053 (17%) of individuals experienced VF by Week 96
- 47 (4%) experienced PDVF

RESISTANCE

- 49 with any VF had resistance testing at baseline & follow-up
- Treatment-emergent resistance was significantly more common in the EFV arm compared with the pooled DTG arms (62% vs 7%; p<0.001)
- Most individuals with emergent resistance had other RAMs at baseline (73%)
- The most common emergent mutations were M184V & K103N

FOLLOW-UP AFTER VF

- 59% of individuals re-suppressed <50 copies/mL within 3 visits (LOCF)
- Significantly more individuals on DTG regimens were able to re-suppress (68% vs 37%; p<0.001)

Table 1. Treatment-emergent mutations in individuals with virological failure by Week 96

	TAF/FTC+DTG (n=351)	TDF/FTC+DTG (n=351)	TDF/FTC/EFV (n=351)
VF*	62 (18%)	66 (19%)	49 (14%)
PDVF*	12 (3%)	16 (5%)	19 (5%)
VF with resistance data	12	16	21
VF with treatment-emergent major mutations:			
NRTI	0/12 (0%)	2/16 (13%)	9/21 (43%)
NNRTI	0/12 (0%)	0/16 (0%)	10/21 (48%)
NRTI or NNRTI	0/12 (0%)	2/16 (13%)	13/21 (62%)
INSTI	0/12 (0%)	0/16 (0%)	0/21 (0%)

*VF=virologic failure defined as either: 1) viral load ≥1000 from 12 weeks; 2) viral load ≥200 from 24 weeks; or 3) viral load ≥50 from 48 weeks. *PDVF=protocol-defined virologic failure defined as 2x ≥1000 from 12 weeks

Figure 1. HIV viral load at point of VF and subsequent three visits. The first column shows the viral load category at the time of VF. The following three columns show the outcome at the subsequent three visits. d/c, early discontinuation of study: EOS, reached end of study (Week 96) & no further visits expected.

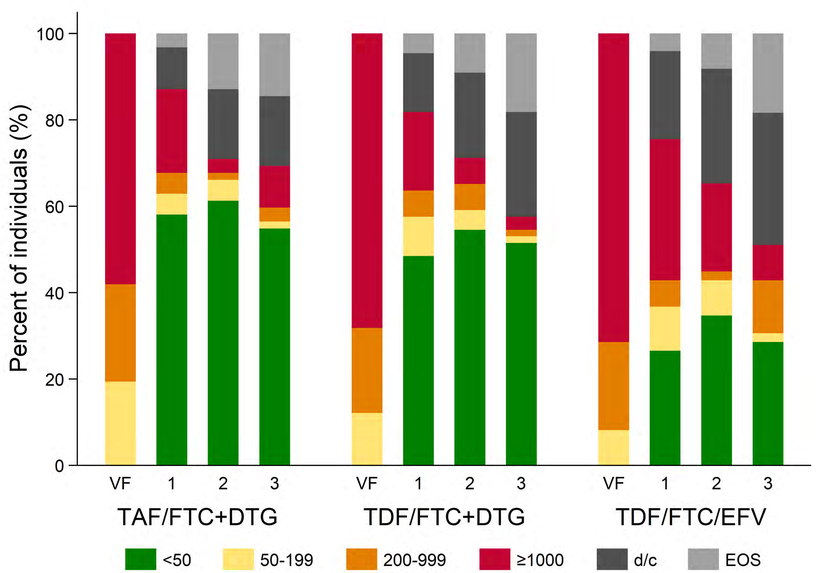

Table 2. HIV over time & mutations in individuals with VF & treatment-emergent NRTI or NNRTI mutations

ID	VL at VF	VL at FU	Baseline mutations	Emergent mutations
TDF/FTC+DTG				
1	156,026	4,481 (d/c)	L100I, K103N	T69TADN, M184MIV
2	30,215	4,466	V106M	M184MV
TDF/FTC/EFV				
3	265	213	K103N, G190A	K101P, K103S, P225PH, K70E, M184V
4	267,142	9,536 (d/c)	V106M	M184MV, G190GA
5	6,278	d/c at VF	V106M, M184V	K65R
6	4,759	d/c at VF		K103N
7	241,875	203,367 (d/c)	P225H	L74V, M184V, L100I, K103N
8	7,294	210		M184V, K103N, P225PH
9	1,361	842	K103N	P225H
10	6,202	<50	Y181V, T215F	M184V, Y188L
11	3,513	583		K103N
12	1,765	482	K101E, K103N, V106M, M184V	D67N, K70R, K219E
13	3,186	<50	Y188L	M184V
14	2,678	110		K103KN
15	26,174	19,590	D67N, K70R, K103N, M184V, K219E	K65R, V106M

VL VF, viral load at viral failure; VL FU – viral load at follow up after VF, including LOCF if censored

CONCLUSIONS -

- **In ADVANCE, there were similar rates of virological failure between the three arms**
- **However, individuals in the TDF/FTC/EFV arm were significantly more likely to develop NRTI or NNRTI mutations by failure (13/21=62%) compared to the DTG arms (2/28=7%) (p<0.001).**
- **11/15 patients with treatment-emergent drug resistance already had NRTI or NNRTI mutations at baseline**
- **Virological failure is often transient with re-suppression observed in 105/177 participants (59%).**
- **Re-suppression <50 copies/mL was more common for individuals on TAF/FTC+DTG or TDF/FTC+DTG (87/128 = 68%) compared with TDF/FTC/EFV (18/49 = 37%) (p<0.001).**

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