



# The FDA Snapshot Algorithm may Overestimate the Efficacy of Initial ART

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## Introduction

- The FDA Snapshot algorithm defines success of antiretroviral therapy (ART) by viral load < 50 copies/mL without ART change (mostly for adverse events [AEs]).
- Notably, a viral load <50 copies/mL but with a drug-related AE is regarded as treatment success. However, drug-related AEs might increase the risk of ART failure, but this has not been demonstrated.
- No recommended ART regimen has demonstrated superiority in those patients with viral load <100,000 copies/mL, who now are the bulk of patients initiating ART.
- We hypothesized that an efficacy algorithm incorporating ART-related AEs that predict subsequent ART failure would be clinically meaningful.

## Methods

- We analyzed individual-patient data from SINGLE, a placebo controlled trial of abacavir-lamivudine-dolutegravir (ABC-3TC-DTG) versus tenofovir-emtricitabine-efavirenz (TDF-FTC-EFV).<sup>1</sup>
- Data were obtained data to week 144 via <https://clinicalstudydatarequest.com> after independent protocol review by the Wellcome Trust (but not the study sponsor).
- We investigated whether any or all grades of drug-related AEs through Week 12 predicted future ART failure (Weeks 48, 96 ± 144) by logistic regression.
- We then investigated failure rates using the Snapshot algorithm vs. a 'Snapshot-Plus' algorithm that additionally regards Grade-2+ drug-related AEs as ART failure.
- Data were analyzed by calculating the proportion of responders (95%CI) with both algorithms. Chi-square and McNemar tests compared responders within and between algorithms, respectively. Randomized arms were compared through Week 144 for all participants, as were strata with viral load ≥ or <100,000 copies/mL at baseline.

## Acknowledgements

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## References

- Walmsley, S. L., et al. (2013). "Dolutegravir plus abacavir-lamivudine for the treatment of HIV-1 infection." *N Engl J Med* 369(19): 1807-1818.

## Results

### Grade 2+ drug-related AE to Week 12 predict subsequent Snapshot failure

- Experiencing any grade 2-4 drug related AE through Week 12 was associated with a significantly increased risk of ART failure at Week 48 by Snapshot (Table 1). This relationship was present when considering all participants, and by baseline viral load strata except at Week 144 in participants with high baseline viral loads.
- In contrast, there was no association with experiencing any-grade drug-related AE through Week 12, and failure by the Snapshot algorithm at Week 48, 96 or 144.

### Differences in proportion of responders by Snapshot and Snapshot-plus

- At Week 48, Snapshot efficacy was 87.9% with ABC-3TC-DTG and 80.6% with TDF-FEV-EFV (Table 2). By Snapshot-plus, response rates were substantially lower (76.6% vs 62.8%, respectively). This pattern was consistent across study weeks and viral load strata.
- The mean difference in DTG vs EFV response rates was greater with 'Snapshot-plus' at each time point, with more significant Chi-square P values by Snapshot-plus algorithm at weeks 48, 96 and 144, overall and in the low viral load stratum.
- In addition, the discordant proportions of responders identified by Snapshot and Snapshot-plus algorithms were significantly different at each study week overall, and in both viral load strata (McNemar's P<0.0001).

Table 1. Odds of failure by Snapshot at Weeks 48, 96 and 144 for participants experiencing any grade, or any grade 2-4, drug-related AE through to Week 12.

WEEK AND GROUP	ANY GRADE AE		GRADE 2-4 AE	
	OR (95%CI)	P	OR (95%CI)	P
<b>All participants</b>				
Week 48	1.07 (0.73 – 1.55)	0.73	2.68 (1.75 – 4.11)	<0.001
Week 96	1.12 (0.82 – 1.55)	0.48	2.55 (1.73 – 3.75)	<0.001
Week 144	1.05 (0.79 – 1.41)	0.74	2.47 (1.76 – 3.58)	<0.001
<b>VL &lt;Slog<sub>10</sub> copies/mL</b>				
Week 48	1.08 (0.67 – 1.76)	0.64	3.00 (1.77 – 5.08)	<0.001
Week 96	1.24 (0.83 – 1.86)	0.30	2.74 (1.72 – 4.37)	<0.001
Week 144	1.08 (0.76 – 1.55)	0.66	2.78 (1.79 – 4.30)	<0.001
<b>VL ≥Slog<sub>10</sub> copies/mL</b>				
Week 48	1.07 (0.59 – 1.94)	0.83	2.47 (1.16 – 5.26)	0.02
Week 96	0.97 (0.57 – 1.65)	0.91	2.44 (1.20 – 4.96)	0.01
Week 144	1.00 (0.60 – 1.65)	0.99	1.93 (0.96 – 3.90)	0.07

Table 2. Odds of failure by Snapshot analysis at Weeks 48, 96 and 144 for study participants experiencing any grade, or any grade 2-4, drug-related AE through to Week 12.

	SNAPSHOT				SNAPSHOT-PLUS				
	% Responders		Mean diff (95%CI)*	Chi-square P	% Responders		Mean diff (95%CI)*	Chi-square P	McNemar's P
<b>All participants</b>	ABC-3TC-DTG (N=414)	TDF-FTC-EFV (N=419)			ABC-3TC-DTG (N=414)	TDF-FTC-EFV (N=419)			
Week 12	83.8	54.2	29.6 (23.7 – 35.6)	<0.0001	76.2	43.4	32.7 (26.4-38.9)	<0.0001	<0.0001
Week 48	87.9	80.6	7.3 (2.3-12.2)	0.004	76.6	62.8	13.8 (7.6-20.0)	<0.0001	<0.0001
Week 96	80.4	72.3	8.1 (2.4-13.9)	0.006	70.3	56.6	13.7 (7.3-20.2)	<0.0001	<0.0001
Week 144	71.5	63.2	8.3 (1.9 – 14.6)	0.01	62.6	50.4	12.2 (5.5-18.9)	<0.004	<0.0001
<b>HIV-RNA &lt;Slog<sub>10</sub> c/mL</b>	N=280	N=288			N=280	N=288			
Week 12	91.8	65.9	25.8 (19.5 – 32.2)	<0.0001	81.8	52.4	29.4 (22.0 – 36.7)	<0.0001	<0.0001
Week 48	90.4	82.6	7.7 (2.1 – 13.3)	0.007	77.9	62.9	15.0 (7.6 – 22.4)	<0.0001	<0.0001
Week 96	85.0	72.6	12.4 (5.8 – 19.1)	0.0003	73.2	55.6	17.7 (9.9 – 25.4)	<0.0001	<0.0001
Week 144	72.9	64.2	8.6 (1.0 – 16.2)	0.03	63.6	50.4	13.2 (5.2 – 21.3)	0.002	<0.0001
<b>HIV-RNA ≥Slog<sub>10</sub> c/mL</b>	N=134	N=131			N=134	N=131			
Week 12	67.2	28.2	38.9 (27.8 – 50.0)	<0.0001	64.2	23.7	40.5 (29.6 – 51.4)	<0.0001	<0.0001
Week 48	82.8	76.3	6.5 (-3.2 to 16.2)	0.19	73.9	62.6	11.3 (0.2 – 22.4)	0.048	<0.0001
Week 96	70.9	71.8	-0.9 (-11.8 to 10.3)	0.87	64.2	58.8	5.4 (-6.3 to 17.1)	0.37	<0.0001
Week 144	68.7	61.1	7.6 (-3.9 to 19.1)	0.20	60.5	50.4	10.1 (1.8 to 22.0)	0.10	<0.0001

\*Mean difference in the proportion of responders in the ABC-FTC-DTG vs TDF-FTC-EFV arm

## Discussion and Conclusion

- Using data from the SINGLE trial, drug-related grade 2+ AEs through Week 12 predicted failure by the Snapshot algorithm at weeks 48, 96 and 144 in all patients, and those with baseline viral load <100,000 copies/mL. This implies that early drug-related AEs are clinically important.
- With 'Snapshot-Plus', between randomized arm differences were greater, and more highly significant in all subjects combined, and also in those with baseline viral loads <100,000 copies/mL.
- There was a significant difference in responder participants identified by each algorithm at each study week and viral load strata.
- Taken together, the results of our analysis suggests the 'Snapshot-plus' algorithm, which also defines failure by experiencing Grade 2+ drug-related AE, may be a more clinically relevant measure of ART efficacy than the current Snapshot algorithm.
- The algorithms should be compared using data from other trials.