Tenofovir Alafenamide versus Tenofovir Disoproxil Fumarate – is there a true difference in efficacy and safety?

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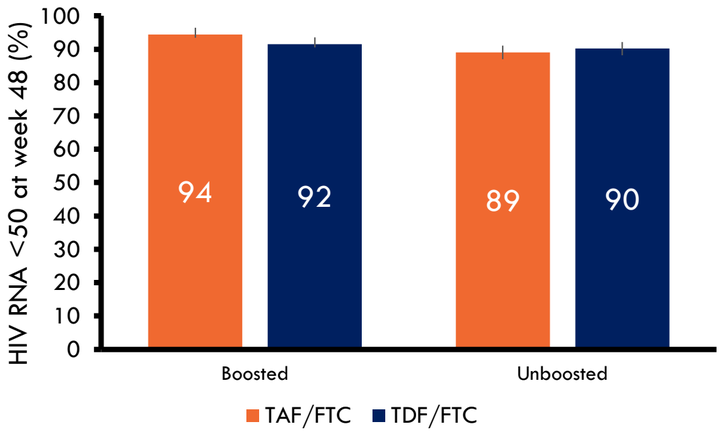
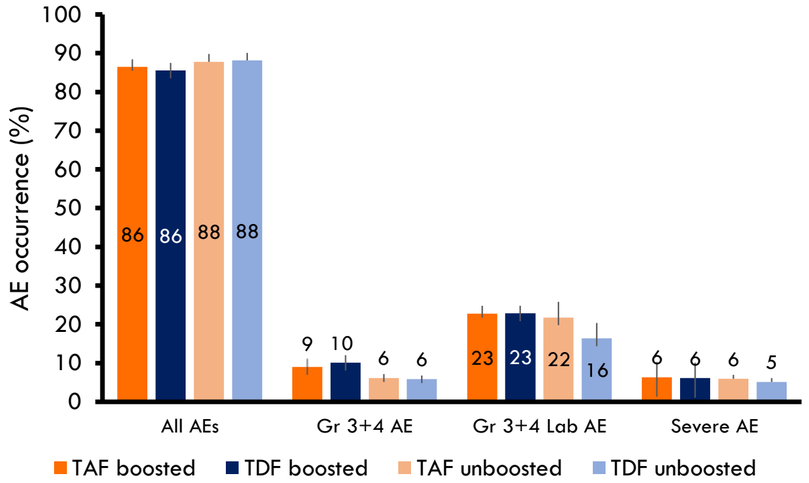
BACKGROUND: Whilst TDF/FTC and TAF/FTC both demonstrate excellent efficacy and safety profiles overall, plasma tenofovir is associated with changes in markers of bone and renal function when used in the treatment of HIV and HBV. Lower plasma and higher intracellular tenofovir concentrations are achieved with tenofovir alafenamide (TAF) than tenofovir disoproxil fumarate (TDF). Pharmacokinetic boosters ritonavir and cobicistat increase plasma tenofovir concentration, compounding existent safety concerns for tenofovir formulations. We assess TAF versus TDF safety with and without booster co-formulation.

METHODS: A previous systematic review was updated with more recently published clinical trials directly comparing TAF or TDF based antiretroviral treatment regimens. TAF and TDF efficacy and safety were then compared in predefined boosted and unboosted subgroups. Efficacy was measured by viral suppression. Key safety endpoints included all AEs, serious AEs, grade 3-4 AEs and AE discontinuation and deaths. Further specific renal (discontinuations and renal tubular AEs) and bone (discontinuations and fractures) markers were also assessed. Overall risk differences for each outcome were calculated using random-effects models with Mantel-Haenszel methods.

Virological Suppression: HIV RNA <50 copies/mL



Safety of TAF versus TDF, boosted and unboosted
Meta-analysis of 14 randomized trials



RESULTS: 14 clinical trials comparing TDF and TAF treatment regimens were identified, 11 of the studies enrolled participants with HIV-1 infection, 2 enrolled people with chronic Hepatitis B infection, and one further trial population was HIV uninfected adults in a study on preventative PrEP usage. The 14 studies report data from 14,894 patients, accounting for a total of 23,723 patient-years of follow-up(PYFU). 6743 patients receiving TDF and 8151 receiving TAF. A total of 6032 patients were participant in the 8 trails assessing boosted regimens, versus 8862 patients in the 6 trails of unboosted regimens.

Regarding efficacy, there was a significant difference (p=0.004) shown in the boosted subgroup, but no difference seen in the unboosted group.

Regarding safety, there were no significant differences, in boosted or unboosted subgroups, between TAF and TDF for any of the key safety endpoints analysed. No differences were seen for the bone markers analysed. No difference was seen overall for the renal markers analysed, however there was a difference in risk for discontinuation due to renal adverse events when boosted (p=0.03), but again no difference when unboosted.

Formulation	Outcome Measure	TAF/FTC Events / Total	%	TDF/FTC Events / Total	%	Effect Estimate - Risk Diff. (C.I.)	p value
Boosted	Viral Suppression	3101 / 3283	94	2210 / 2415	92	2% (1% to 4%)	0.0004
	All Adverse Events	3023 / 3498	86	2157 / 2523	86	1% (-1% to 3%)	n.s
	Gr 3+4 AE	313 / 3498	9	254 / 2523	10	-1% (-2% to 1%)	n.s
	Gr 3+4 Lab AE	516 / 2270	23	395 / 1732	23	0% (-5% to 4%)	n.s
	SAE	221 / 3498	6	154 / 2523	6	0% (-1% to 1%)	n.s
	Deaths	2 / 3283	0	3 / 2415	0	0% (0% to 0%)	n.s
	Bone Fractures	22 / 3498	1	16 / 2523	1	0% (0% to 0%)	n.s
	Renal Tubule AE	0 / 3498	0	3 / 2523	0	0% (0% to 0%)	n.s
	DC A/E	44 / 3386	1	50 / 2465	2	-1% (-2% to 0%)	n.s
	D/C Bone	0 / 2529	0	0 / 1606	0	0% (0% to 0%)	n.s
	D/C Renal	3 / 3395	0	12 / 2473	0	0% (-1% to 0%)	0.03
Unboosted	Viral Suppression	984 / 1105	89	994 / 1102	90	-1% (-3% to 1%)	n.s
	All Adverse Events	4094 / 4665	88	3724 / 4227	88	1% (-1% to 3%)	n.s
	Gr 3+4 AE	286 / 4665	6	246 / 4227	6	0% (-2% to 2%)	n.s
	Gr 3+4 Lab AE	429 / 1971	22	251 / 1534	16	2% (-3% to 6%)	n.s
	SAE	278 / 4665	6	218 / 4227	5	1% (-1% to 2%)	n.s
	Deaths	4 / 4665	0	4 / 4227	0	0% (0% to 0%)	n.s
	Bone Fractures	21 / 1971	1	18 / 1534	1	0% (-1% to 0%)	n.s
	Renal Tubule AE	0 / 1620	0	0 / 1183	0	0% (0% to 0%)	n.s
	D/C AE	64 / 4665	1	64 / 4227	2	0% (0% to 0%)	n.s
	D/C Bone	1 / 1971	0	0 / 1534	0	0% (0% to 0%)	n.s
	D/C Renal	3 / 4665	0	6 / 4227	0	0% (0% to 0%)	n.s

CONCLUSIONS: Ritonavir-/cobicistat-boosted TDF was associated with lesser comparative efficacy than boosted TAF. However, the overall TAF and TDF efficacy differences were marginal. TAF showed higher risk of renal event discontinuation, but only on boosted regimens. Both TAF and TDF have favourable efficacy and safety profiles and the broadcasted health economic benefits of TAF versus generic TDF may be reduced without boosters.
Most TDF regimens are unboosted globally. It is therefore inappropriate to combine boosted and unboosted results in analyses.

KEY POINTS:

- Overall no differences in any safety or efficacy endpoints between TAF and TDF when used unboosted
- The only differences seen between TAF and TDF were for efficacy and renal discontinuations and these were only on boosted regimens
- TAF and TDF are mainly used unboosted worldwide. Results from boosted studies are becoming less relevant to modern clinical practice