Efficacy and safety of tenofovir disoproxil fumarate versus low-dose stavudine over 96 weeks: a multi-country randomised, non-inferiority trial

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Objective: To determine whether dose reduction of stavudine (d4T) reduces drug toxicity, while preserving treatment efficacy, and document tenofovir disoproxil fumarate (TDF) toxicity.

Methods: Phase 4, 96-week, randomised, double-blind, non-inferiority trial in India, South Africa and Uganda. D4T 20 mg BD was compared with TDF, taken in combination with lamivudine (3TC) and efavirenz (EFV) in 1072 HIV-1-infected treatment-naïve adults. There was no screening for drug resistance at baseline. The primary endpoint was the proportion of participants with HIV-1 RNA < 50 copies/mL at Week 96. Adverse events assessments included measures of bone density and body fat. The trial is registered on Clinicaltrials.gov (NCT02670772).

Results: Between 07/2012 and 01/2014, 536 participants were recruited per arm. At Week 96, trial completion rates were 75.7% with d4T/3TC/EFV (n=406) and 82.1% with TDF/3TC/EFV (n=440). Non-completion was largely due to virological failure (6.2% [33] with d4T/3TC/EFV versus 5.4% [29] with TDF/3TC/EFV; p=0.60). For the primary endpoint of HIV-1 RNA suppression < 50 copies/mL at Week 96, d4T/3TC/EFV was non-inferior to TDF/3TC/EFV (79.3%, 425/536 versus 80.8% 433/536; difference = -1.49%, 95%CI = (-6.3 +3.3). In a sub-study, there was no correlation between drug resistance and the risk of virological failure. Drug-related adverse event discontinuations were higher with d4T (6.7%, n=36) than TDF (1.1%, n=6; p<0.001). Lipodystrophy was more common in the d4T (5.6%) than TDF arm (0.2%). Drug-related adverse event discontinuations were higher with d4T (6.7%), than TDF (1.1%). Creatinine clearance increased in both arms, by 18.1 mL/min in the d4T arm and 14.2 mL/min with TDF (p=0.03). Bone density, however, showed greater loss at the hip with TDF.

Conclusions: In this 96-week randomised trial in 1072 treatment naïve patients, low-dose d4T combined with 3TC/EFV demonstrated non-inferior virological efficacy compared to TDF/3TC/EFV, but mitochondrial toxicity remained high. Little renal toxicity was noted in either arm.

Figure 1: Study flowchart

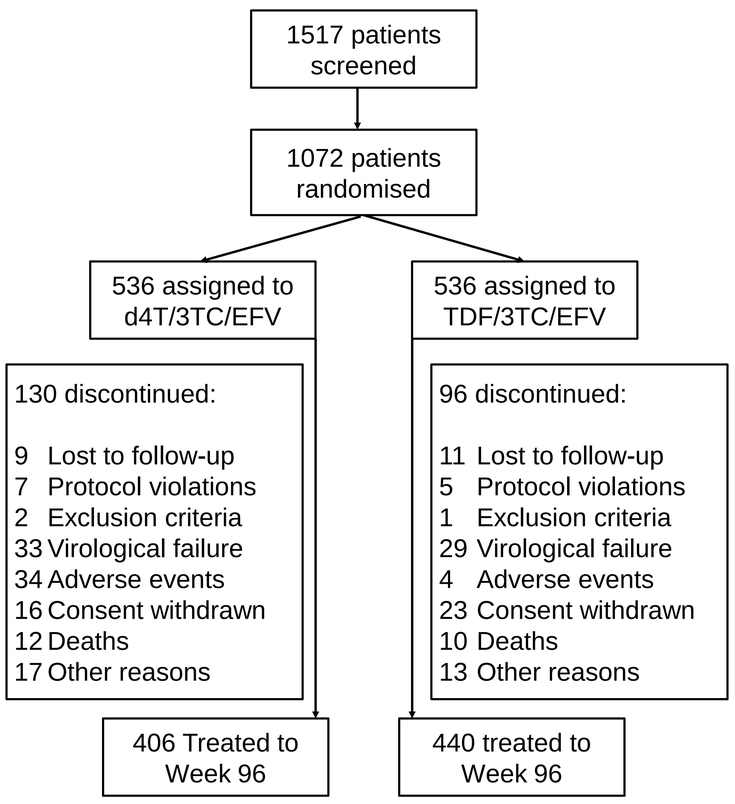


Table 1: Baseline characteristics

Baseline data		d4T/3TC/EFV n=536	TDF/3TC/EFV n=536
Age (years, mean (SD))		35.5 (8.4)	35.0 (8.1)
Sex (n, %):	Female	326 (61%)	293 (55%)
Race (n,%):	Black African	492 (92%)	492 (91%)
	Indian	43 (8%)	43 (8%)
	Other	1 (0.2%)	1 (0.2%)
Country (n, %):	South Africa	300 (56%)	300 (56%)
	Uganda	193 (36%)	193 (36%)
	India	43 (8%)	43 (8%)
Prior or current TB (n, %)		76 (14%)	86 (16%)
Weight (kg, median (IQR))		62 (54-70)	62 (55-70)
BMI (kg/m^2, median (IQR))		23 (20-27)	23 (21-26)
Underweight (BMI< 18.5, n (%))		54 (10%)	33 (6%)
CD4 count (cells/uL, median (IQR))		206 (128-274)	206 (123-270)

Table 2: Treatment-emergent, drug-related adverse events

Adverse events	d4T/3TC/EFV n=536	TDF/3TC/EFV n=536
Discontinuation for adverse events	52 (10%)	19 (4%) *
Patients with 1 or more drug-related Adverse Events (n, %)	166 (31%)	129 (24%) *
Type of Adverse Event (at least 3%):		
Dizziness	176 (33%)	175 (33%)
Upper RTI	72 (14%)	99 (19%)
Weight decreased	77 (14%)	86 (16%)
Urinary tract infection	69 (13%)	91 (16%)
Peripheral neuropathy	37 (7%)	24 (4%)
Lipodystrophy	30 (6%)	1 (0.2%) *
Lower RTI	32 (6%)	30 (4%)
Somnolence	27 (5%)	24 (4%)
Nausea	20 (4%)	25 (5%)
Vomiting	20 (4%)	31 (6%)
Asthenia	21 (4%)	11 (2%)
Gastritis	15 (3%)	3 (0.6%) *
Pyrexia	26 (5%)	12 (2%)
Appetite decreased	25 (4%)	18 (3%)
Abnormal dreams	14 (3%)	20 (4%)

* p<0.01 for difference between d4T and TDF treatment arms;
RTI, respiratory tract infection

Table 3: Change in Bone Density (DEXA)

DEXA test		d4T/3TC/EFV n=536	TDF/3TC/EFV n=536
Hip t-score < -1 (n, %)			
	Baseline	82/531 (15%)	110/532 (21%)
	Week 24	86/494 (17%)	123/489 (25%) *
	Week 48	97/448 (22%)	127/453 (28%)
	Week 96	93/396 (24%)	137/427 (32%) *
Hip t-score change (median, IQR)			
	Week 24	-0.06 (-0.15, 0.03)	-0.14 (-0.24, -0.05) *
	Week 48	-0.13 (-0.25, -0.01)	-0.24 (-0.37, -0.11) *
	Week 96	-0.20 (-0.35, -0.06)	-0.28 (-0.45, -0.14) *
Lumbar spine t score < -1 (n, %)			
	Baseline	251/527 (48%)	244/529 (46%)
	Week 24	261/494 (53%	269/486 (55%)
	Week 48	248/449 (55%)	248/450 (55%)
	Week 96	219/396 (55%)	241/426 (57%)
Lumbar spine t-score change (median, IQR)			
	Week 24	-0.15 (-0.31. 0.00)	-0.28 (-1.61, -0.1) *
	Week 48	-0.15)-0.34, +0.03)	-0.27 (-0.49, -0.11) *
	Week 96	-0.17 (-0.43, +0.02)	-0.31 (-0.55, -0.09) *

Table 4: Change in Body Fat (DEXA)

DEXA test		d4T/3TC/EFV n=536	TDF/3TC/EFV n=536
Limb fat (kg, median, IQR)			
	Baseline	8.3 (5.3, 12.3)	8.0 (4.9, 11.6)
	Week 24	9.1 (5.8, 13.3)	8.7 (5.2, 12.2)
	Week 48	8.5 (5.6, 12.4)	8.9 (5.6, 13.1)
	Week 96	7.6 (4.9, 11.2)	9.1 (5.9, 13.6) *
Limb fat change (median, IQR)			
	Week 24	+0.6 (-0.3, +1.7)	+0.3 (-0.5, +1.3) *
	Week 48	+0.4 (-1.1, +2.0)	+0.9 (-0.4, +2.3) *
	Week 96	-0.1 (-2.0, +1.7)	+1.2 (-0.2, +2.9) *
Trunk fat (kg, median, IQR)			
	Baseline	5.9 (3.5, 9.1)	5.5 (3.4, 8.9)
	Week 24	6.8 (3.9, 10.1)	6.1 (3.6, 9.6)
	Week 48	7.1 (4.5, 10.8)	6.7 (4.0, 10.6)
	Week 96	7.3 (4.5, 10.9)	7.2 (4.5, 11.4)
Trunk fat change (median, IQR)			
	Week 24	+0.6 (-0.3, +1.5)	+0.2 (-0.7, +1.2) *
	Week 48	+1.0 (-0.2, +2.6)	+0.7 (-0.5, +2.3)
	Week 96	+1.5 (+0.1, +3.0)	+1.2 (-0.3, +3.2)

- p<0.01 for difference between d4T and TDF treatment arms

Table 5: HIV RNA suppression by treatment arm

Endpoint	d4T/3TC/EFV n=536	TDF/3TC/EFV n=536
HIV RNA < 50 copies/mL, Week 48		
ITT analysis all patients	425/536 (79.3%)	433/536 (80.8%)
Baseline RNA < 100,000	226/271 (83.4%)	254/306 (83.0%)
Baseline RNA > 100,000	199/262 (76.0%)	179/228 (78.5%)
Baseline CD4 < 200 c/uL	194/249 (77.9%)	198/259 (76.4%)
Baseline CD4 > 200/uL	231/284 (81.3%)	235/275 (85.5%)
Per Protocol analysis	421/451 (93.3%)	430/459 (93.7%)
HIV RNA <200 copies/mL, Week 96		
ITT analysis all patients	391/536 (72.9%)	426/536 (79.5%)
Per protocol analysis	387/451 (85.8%)	418/459 (91.1%)

Key Messages

This is one of the largest studies of first-line TDF/3TC/EFV conducted. 536 patients were evaluated on TDF/3TC/EFV for 96 weeks.

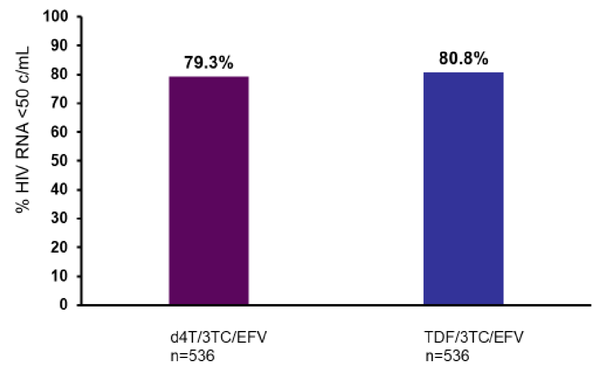
The comparison with d4T/3TC/TDF is of limited interest – d4T is no longer recommended in treatment guidelines. There was significantly more lipoatrophy in the d4T/3TC/EFV arm.

After 48 weeks of treatment, 81% of patients randomised to TDF/3TC/EFV had HIV RNA suppression > 50 copies/mL. Patients in this trial were not tested for drug resistance at baseline, and the prevalence of transmitted NRTI/NNRTI drug resistance in South Africa is approximately 10%.

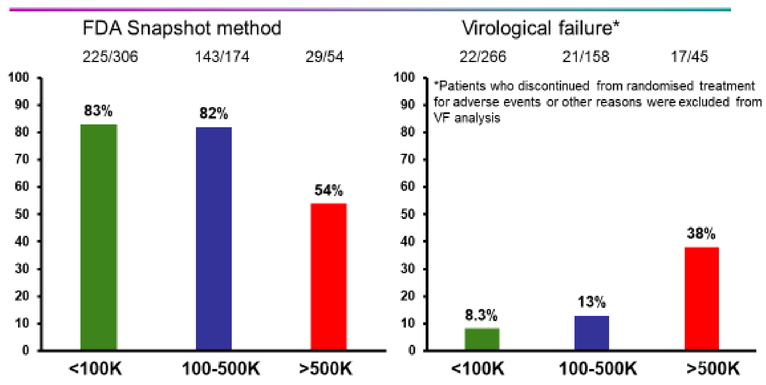
There was a subset of patients with very high baseline HIV RNA (> 500,000 copies/mL) who showed high rates of virological failure.

This same correlation between high baseline HIV RNA > 500,000 copies/mL and lower efficacy has been seen in other randomised trials of first-line TDF/XTC/EFV, and also with first-line DTG and RAL-based triple combination treatment.

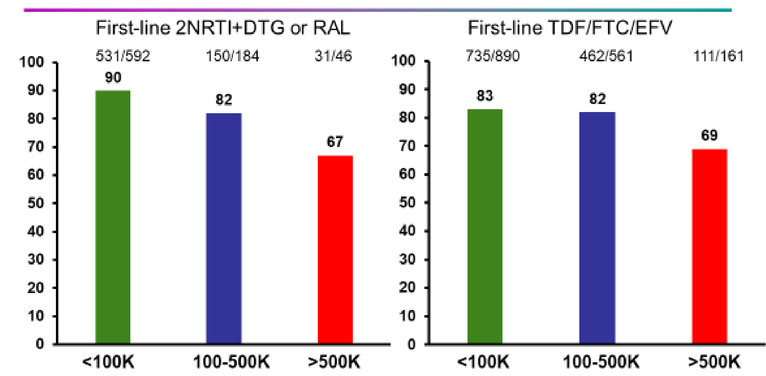
Primary efficacy analysis
HIV RNA<50 copies/mL, Week 48, FDA Snapshot



TDF/3TC/EFV arm: Efficacy by baseline HIV RNA
HIV RNA<50 copies/mL, Week 96



Other studies: efficacy by baseline HIV RNA >500K
HIV RNA<50 copies/mL, Week 48, FDA Snapshot



SPRING-2
Overall trial results, n=822

STAR, ECHO, THRIVE, WRHI-001
Combined results, n=1612