A Review of the Virological Efficacy of the Four Tenofovir-Containing WHO-Recommended Regimens for Initial HIV Therapy

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INTRODUCTION

The 2010 WHO ARV Treatment guidelines recommend phasing out d4T and adding four new options for first-line therapy: TDF/3TC/NVP, TDF/FTC/NVP, TDF/3TC/EFV, and TDF/FTC/EFV. TDF is more potent and less toxic than AZT and d4T. It is not known, however, whether the four WHO-recommended, TDF-containing regimens are equally efficacious or even whether each offers an improvement over the older dual NRTI / NNRTI regimens. Therefore, we reviewed published studies of the virological efficacy of each of these regimens for first-line therapy.

METHODS

- To identify studies assessing the efficacy of WHO-recommended, TDF-containing first-line ARV regimens, we searched for papers and meeting abstracts that included prospective or retrospective studies of these four treatment regimens. We excluded (i) studies comprising ARV-experienced patients (ii) studies lacking virological efficacy results (iii) studies for which the # of individuals receiving each regimen was unknown (iv) studies containing ten or fewer subjects.
- Results for treatment failure, virological failure and genotypic resistance (if available)were extracted for each study. Treatment failure is generally defined as those subjects who did not achieve the pre-defined virological endpoint for any reason. Virological failure (VF) is defined as those who failed due to poor virological response.

RESULTS

- We screened 330 publications and 1,323 conference abstracts. 29 publications met study criteria: TDF/3TC/NVP (3 studies), TDF/FTC/NVP (8 studies), TDF/3TC/EFV (6 studies), TDF/FTC/EFV (14 studies). Tables 1-4 describe all evaluable studies in detail. Figure 1 presents RR and 95%CI for treatment failure and VF for comparative studies.
- TDF/3TC/NVP was associated with a higher risk of virological failure in comparison to AZT/3TC/NVP in two studies (Figure 1), and was prematurely discontinued in a pilot study due to high rates of VF and drug resistance (Table 1).
- TDF/FTC/NVP had VF rates similar to those of the comparator arm with the exception of two retrospective studies and one very small prospective study.
- TDF/3TC/EFV, and TDF/FTC/EFV were equivalent or superior to their comparators.
- Of subjects with genotypic resistance tests, K65R occurred in 7/16 (44%) of those receiving TDF/3TC/NVP, 16/40 (40%) of those receiving TDF/FTC/NVP, 15/44 (34%) of those receiving TDF/3TC/EFV, and 4/114 (1%) of those receiving TDF/FTC/EFV.

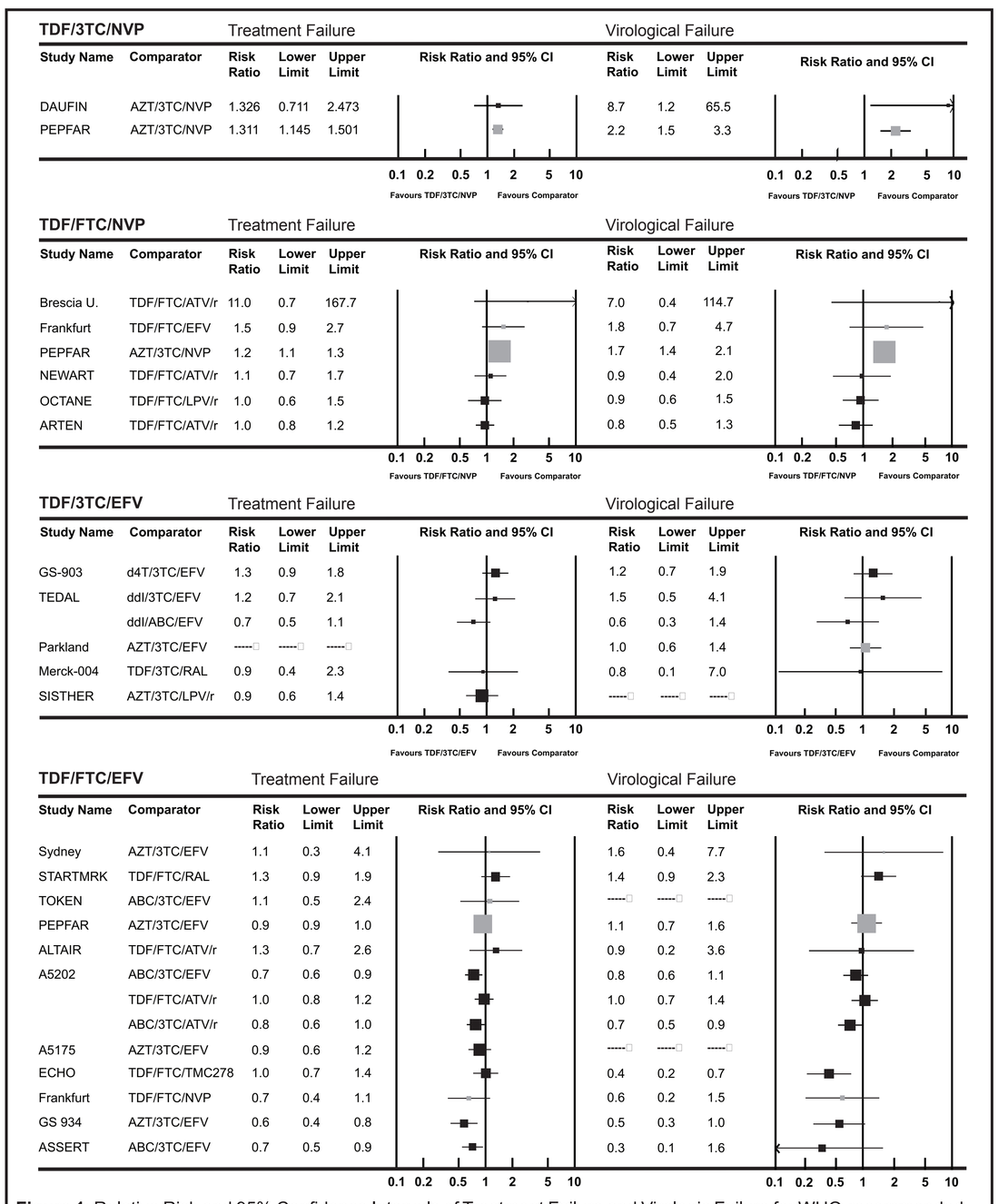

Figure 1: Relative Risk and 95% Confidence Intervals of Treatment Failure and Virologic Failure for WHO-recommended, TDF-containing regimens vs comparator regimens from prospective randomized trials (black points) and retrospective cohort studies (gray points). Studies of non-FDA approved drugs and regimens were not included. Further details of the studies can be found in Tables 1-4.

DISCUSSION AND CONCLUSIONS

- TDF/3TC/NVP is the least well-studied of the four TDF-containing, WHO-recommended regimens, and demonstrated poor virological efficacy in the three available studies.
- TDF/FTC/NVP was as efficacious as TDF/FTC plus a boosted PI in three prospective studies but was associated with a higher risk of VF than AZT/3TC/NVP in one large retrospective study. In contrast, TDF/3TC/EFV and TDF/FTC/EFV were uniformly associated with high clinical and virological responses.
- Plausible explanations for the possible inferiority of TDF/3TC/NVP compared with AZT/3TC/NVP and the remaining TDF-containing regimens include:

  (i) The greater in vitro and in vivo activity of EFV compared with NVP.

  (ii) The longer intra-cellular half-life of FTC in comparison to 3TC.

  (iii) Once-daily NVP and 3TC are associated with decreased trough concentrations and might increase risk of virological failure if individual drug dosages are missed.

  (iv) TDF/3TC/NVP may have a lower genetic barrier to resistance as evidenced by the high proportion of patients with K65R and NNRTI resistance.
- The apparent inferiority of TDF/3TC/NVP compared with AZT/3TC/NVP despite the greater antiretroviral activity and lower toxicity of TDF compared with AZT underscores the concept that ARV regimens are more than the sum of their parts.
- The U.S. DHHS treatment guidelines state that TDF/3TC/NVP may be an acceptable first line regimen but should be used with caution. Because patients in resource-limited regions undergo less laboratory monitoring and are at higher risk of developing drug resistance than patients in well-resourced regions, further study of TDF/3TC/NVP is urgently required before this regimen is widely deployed for initial ARV therapy.

Table 1: Studies of Tenofovir (TDF) / Lamivudine (3TC) / Nevirapine (NVP) for Initial ART

Reference	Study Design (VL Endpoint)	Regimen	No.	CD4	VL	Wks	Rx Failure	VF	VF p-value	Genotypic Resistance Testing (GRT)
DAUFIN (Rey et al 2009)	Prospective OL randomized trial (VL >2 log10) by wk 12 and <400 through wk 96)	TDF/3TC/NVP (QD)	36	191	5.0	12	15 (42%)	9 (25%)	0.01	Prematurely terminated by wk 12. Subjects on TDF/3TC/NVP developed NRTI+NNRTI DRMs including 6 with 65R.
		AZT/3TC/NVP (BID)	35	195	4.9	12	11 (31%)	1 (3%)		
Nigerian PEPFAR (Scarsi et al 2010)	Retrospective cohort study (VL <1,000 at wk 24)	TDF/3TC/NVP (BID)	285	132	4.6	48	126 (44%)	22/103 (21%)	<0.001	NA
		AZT/3TC/NVP (BID)	5925	147	4.6	48	1998 (34%)	207/2174 (10%)		
Boehringer-Ingelheim (Towner et al 2004)	Prospective OL pilot trial (VL<75 at wk 24)	TDF/3TC/NVP (QD)	23	169	5.2	24	13 (57%)	7 (30%)	NA	Prematurely terminated due to hVF, which occurred in 7/8 subjects with baseline VL ≥100,000. The 7 subjects with VF had NRTI & NNRTI DRMs. 65R occurred in 1 subject.

Table 2: Studies of Tenofovir (TDF) / Emtricitabine (FTC) / Nevirapine (NVP) for Initial ART

Reference	Study Design (VL Endpoint)	Regimen	No.	CD4	VL	Wks	Rx Failure	VF	VF p-value	Genotypic Resistance Testing (GRT)
Brescia University (Lapadula et al 2008)	Prospective randomized trial (VL 1log by wk 12)	TDF/FTC/NVP (BID)	7	132	5.1	12	5 (71%)	3 (42%)	0.2	The 3 TDF/FTC/NVP subjects with VF had NRTI+NNRTI DRMs including 1 with 65R.
		TDF/FTC/ATVr (QD)	7	190	5.1	12	0 (0%)	0 (0%)		
ARTEN (Soriano et al 2009)	Prospective OL randomized trial (VL<50 at wk 48)	TDF/FTC/NVP (QD and BID arms)	376	182	5.1	48	125 (33%)	44 (12%)	0.4	29 subjects in combined NVP arms had NRTI ± NNRTI DRMs including 12 with 65R. No ATVr subjects had DRMs
		TDF/FTC/ATVr (QD)	193	188	5.1	48	67 (35%)	28 (15%)		
NEWART (DeJesus et al 2010)	Prospective OL randomized trial (VL<50 at wk 48)	TDF/FTC/NVP (BID)	75	176	4.9	48	29 (39%)	11 (15%)	>0.5	19/23 pooled subjects with VF had GRT. Six had NNRTI and NRTI DRMs, including 2 with 65R, 3 with 184I/V.
		TDF/FTC/ATVr (QD)	77	193	4.9	48	27 (35%)	12 (16%)		
VERxVE (Gathe et al 2010)	Prospective randomized trial (VL<50 at wk 48)	TDF/FTC/NVP IR (BID)	506	227	4.7	48	97 (19%)	26 (5%)	>0.5	NA
		TDF/FTC/NVP XR (QD)	505	229	4.7	48	84 (17%)	24 (5%)		
OCTANE Trial 2 (Lockman et al 2010)	Prospective OL randomized trial (VL <400 at wk 24)	TDF/FTC/NVP (BID)	249	121	5.2	72	34 (14%)	29 (12%)	>0.5	NA
		TDF/FTC/LPVr (BID)	251	121	5.2	72	36 (14%)	32 (13%)		
Nigerian PEPFAR (Scarsi et al 2010)	Retrospective cohort study (VL <1,000 at wk 24)	TDF/FTC/NVP (BID)	1852	137	4.7	48	761 (41%)	104/646 (16%)	<0.001	NA
		AZT/3TC/NVP (BID)	5925	146	4.6	48	1998 (34%)	207/2174 (10%)		
Frankfurt Cohort (Stephan et al 2009)	Retrospective cohort study (VL<50 at wk 48)	TDF/FTC/NVP (BID)	72	201	4.8	48	23 (32%)	10 (13%)	0.2	NA
		TDF/FTC/EFV	77	208	5.1	48	16 (21%)	6 (8%)		
Nevada Group (Vallecillo et al 2009)	Retrospective cohort study (VL<50 at wk 48)	TDF/FTC/NVP (BID)	123	215	4.8	48	27 (22%)	8 (7%)	NA	In 8 subjects with VF, 6 had 184V, 5 had ≥1 NNRTI DRM, and 3 had 65R.

Table 3: Studies of Tenofovir (TDF) / Lamivudine (3TC) / Efavirenz (EFV) for Initial ART

Reference	Study Design (VL Endpoint)	Regimen	No	CD4	VL	Wks	Rx Failure†	VF	VF p-value	Genotypic Resistance Testing (GRT)
GS-903 (Gallant et al 2004)	Prospective randomized trial (VL<400 at wk 48)	TDF/3TC/EFV	299	276	4.9	48	60 (20%)	29 (10%)	0.3	Of 29 TDF subjects with VF, 16 had ≥1 NNRTI DRM, 12 had 184V, and 7 had 65R. Of 25 d4T subjects with VF, 12 had ≥1 NNRTI DRM, 8 had 184V, 2 had 65R.
		d4T/3TC/EFV	301	283	4.9	48	48 (16%)	25 (8%)		
Merck-004 (Markowitz et al 2007)	Prospective randomized trial (VL <50 at wk 48)	TDF/3TC/EFV	38	280	4.8	48	5 (13%)	1 (3%)	>0.5	The EFV subject with VF had ≥1 NNRTI DRM, 184V, 65R. Two RAL subjects with VF had ≥ 1 RAL
		TDF/3TC/RAL (BID)	160	305	4.8	48	23 (14%)	5 (3%)		
TEDAL (Maggiolo et al 2006)	Prospective randomized trial (VL <50 at wk 48)	TDF/3TC/EFV	64	203	5.3	48	21 (33%)	8 (13%)	>0.5	All 27 subjects with VF had NRTI +/- NNRTI DRMS. 5 TDF subjects had 65R.
		DDI/3TC/EFV	72	172	5.4	48	19 (26%)	6 (8%)		
		DDI/ABC/EFV	63	183	5.3	48	29 (46%)	13 (21%)		
Parkland (Keiser et al 2005)	Retrospective cohort study (VL<400 at wk 48)	TDF/3TC/EFV	163	NA	4.8	48	NA	28 (17%)	>0.5	NA
		AZT/3TC/EFV	313	NA	4.5	48	NA	56 (18%)		
SISTHER Substudy (Torti et al 2005)	Prospective randomized trial (VL<50 at wk 52)	TDF/3TC/EFV	83	194	5.3	28	26 (30%)	NA	>0.5	2/5 TDF/3TC/EFV subjects with GRT had 65R. No DRMs occurred with AZT/3TC/LPV/r.
		AZT/3TC/LPV/r (BID)	91	194	5.3	28	32 (38%)	NA		
Elvucitabine Phase II trial (DeJesus et al 2008)	Prospective randomized trial (VL<50 at wk 48)	TDF/3TC/EFV	37	325	4.8	96	8 (22%)	1/30 (3%)	>0.5	The EFV and ELV subjects with VF each had ≥1 NNRTI DRM. The EFV subject also had 184V.
		TDF/ELV/EFV (QD)	37	325	4.8	96	13 (35%)	1/25 (4%)		

Table 4. Studies of Tenofovir (TDF) / Emtricitabine (FTC) / Efavirenz (EFV) for Initial ART

Reference	Study Design (VL Endpoint)	Regimen	No.	CD4	VL	Wks	Rx Failure	VF	VF p-value	Genotypic Resistance Testing (GRT)
GS-934 (Gallant et al 2006)	Prospective randomized trial (VL<400 at wk 48)	TDF/FTC/EFV	244	233	5.0	48	38 (16%)	12 (5%)	0.08	9/12 subjects with VF on TDF/FTC/EFV had DRMs. 9 had NNRTI DRMs, 2 had 184V, none had 65R. 17 of 23 subjects on AZT/3TC/EFV with VF had DRMs. 16 had NNRTI DRMs, 7 had 184V.
		AZT/3TC/EFV	243	241	5.0	48	66 (27%)	23 (9%)		
STARTMRK (Lennox et al 2009)	Prospective randomized trial (VL<50 at wk 48)	TDF/FTC/EFV	282	217	5.0	48	52 (18%)	39 (14%)	0.15	Of 39 subjects with VF on TDF/FTC/EFV, 3 had NNRTI-DRMs and 1 had 184V. Of the 27 with VF on TDF/FTC/RAL, 4 had RAL-DRMs and 3 had 184V.
		TDF/FTC/RAL	281	219	5.0	48	40 (14%)	27 (10%)		
ACTG 5202 (Daar et al 2010; Daar et al 2011; Sax et al 2009)	Prospective randomized trial (VL<200 at wk 24)	TDF/FTC/EFV	464	234	4.7	48	97 (21%)	57 (12%)	0.02	Of 57 subjects with VF on TDF/FTC/EFV, 27 had NNRTI DRMs, 5 had 184V and 4 had 65R. Of 72 subjects with VF on ABC/3TC/EFV, 41 had NNRTI DRMs, 22 had 184V and 3 had
		ABC/3TC/EFV	465	225	4.7	48	132 (28%)	72 (15%)		
		TDF/FTC/ATVr	465	224	4.7	48	101 (23%)	57 (12%)		
		ABC/3TC/ATVr	463	236	3.6	48	125 (27%)	83 (18%)		
ASSERT (Post et al 2010)	Prospective randomized trial (VL<50 at wk 48)	TDF/FTC/EFV	193	230	5.1	48	56 (29%)	2 (1%)	0.2	No subjects on TDF/FTC/EFV had DRMs. Of 6 subjects with VF on ABC/3TC/EFV, 3 had NNRTI-DRMs, and 1 had 65R.
		ABC/3TC/EFV	192	240	5.0	48	78 (41%)	6 (3%)		
ALTAIR (Puls et al 2010)	Prospective randomized trial (VL<50 at wk 48)	TDF/FTC/EFV	114	227	4.7	48	17 (10%)	4 (4%)	>0.5	Of 4 subjects with VF on TDF/FTC/EFV, 1 had NNRTI DRMs,1 had 184V. Of 11 subjects with VF on TDF/FTC/AZT/ABC, 2 had DRMs; 1 with 65R, 1 with 184V + a TAM. Of 4 subjects with VF on TDF/FTC/ATV/r 1 had 184V.
		TDF/FTC/ATVr	105	235	4.8	48	12 (8%)	4 (4%)		
		TDF/FTC/AZT/ABC	103	226	4.6	48	28 (24%)	11 (11%)		
ACTG 5175 (PEARLS) (Campbell et al 2011)	Prospective randomized trial (VL<400 at wk 48)	TDF/FTC/EFV	526	162	5.0	48	68 (13%)	NA	>0.5	NA
		AZT/3TC/EFV	519	169	5.1	48	78 (15%)	NA		
ECHO (Cohen et al 2010)	Prospective randomized trial (VL<50 at wk 48)	TDF/FTC/EFV	344	NA	NA	48	59 (17%)	15 (4%)	>0.5	NA
		TDF/FTC/TMC278	346	NA	NA	48	59 (17%)	38 (11%)		
QUAD Study (Cohen et al 2011)	Prospective randomized trial (VL<50 at wk 48)	TDF/FTC/EFV	23	436	4.58	48	1 (5%)	0	>0.5	No genotypic resistance reported
		EVG/COBI/TDF/FTC	48	354	4.59	48	2 (4%)	0		
Nigerian PEPFAR (Darin et al 2010)	Retrospective cohort study (VL<1000 at wk 24, confirmed by wk 48)	TDF/FTC/EFV	1330	136	4.7	48	552/1330 (41%)	40/386 (10%)	>0.5	No genotypic resistance reported
		AZT/3TC/EFV	1575	136	4.7	48	704/1575 (45%)	45/458 (10%)		
ANRS Senegal (Landman et al 2009)	Prospective pilot trial (VL<50 at wk 48)	TDF/FTC/EFV	40	111	5.3	48	11(28%)	7 (17%)	NA	NA
Frankfurt Cohort (Stephan et al 2009)	Retrospective cohort study (VL<50 at wk 48)	TDF/FTC/EFV (QD)	77	208	5.1	48	16 (21%)	6 (8%)	0.2	NA
		TDF/FTC/NVP (BID)	72	201	4.8	48	23 (32%)	10 (13%)		
TOKEN Study (Das et al 2008)	Retrospective cohort study (VL<40 at wk 48)	TDF/FTC/EFV	81	172	5.4	48	14 (17%)	NA	>0.5	NA
		ABC/3TC/EFV	58	172	5.4	48	9 (15%)	NA		
Sydney Clinic (Malhotra et al 2007)	Retrospective cohort study (VL undetectable at wk 48)	TDF/FTC/EFV	17	237	5.0	48	4 (24%)	4 (22%)	>0.5	NA
		AZT/3TC/EFV	14	175	4.7	48	3 (19%)	2 (11%)		
1-pill vs. 2-pill TDF/FTC/EFV (Perez-Valero et al 2010)	Retrospective cohort study	TDF/FTC/EFV (1-pill)	59	250	4.5	48	7(12%)	NA	0.2	NA
		TDF/FTC/EFV (2-pill)	79	244	4.5	48	4 (5%)	NA		