# A Review of the Virological Efficacy of the 4 World Health Organization–Recommended Tenofovir-Containing Regimens for Initial HIV Therapy

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**(See the Editorial Commentary by Kuritzkes et al, on pages 876–7.)**

We systematically reviewed studies of the virological efficacy of the 4 new tenofovir (TDF)-containing regimens recommended for initial antiretroviral (ARV) therapy in the 2010 World Health Organization ARV Treatment Guidelines. Thirty-three studies assessed the efficacy of 1 or more TDF-containing regimens: TDF/lamivudine (3TC)/nevirapine (NVP) (n = 3), TDF/ emtricitabine (FTC)/NVP (n = 9), TDF/3TC/efavirenz (EFV) (n = 6), and TDF/FTC/EFV (n = 19). TDF/3TC/NVP was the least well-studied and appeared the least efficacious of the 4 regimens. In 2 comparative studies, TDF/3TC/NVP was associated with significantly more virological failure than AZT/3TC/NVP; a third study was terminated prematurely because of early virological failure. TDF/FTC/NVP was either equivalent or inferior to its comparator arms. TDF/3TC/EFV was equivalent to its comparator arms. TDF/FTC/EFV was equivalent or superior to its comparator arms. Possible explanations for these findings include the greater antiviral activity of EFV versus NVP and longer intracellular half-life of FTC-triphosphate versus 3TC-triphosphate. Further study of TDF/3TC/NVP is required before it is widely deployed for initial ARV therapy.

The initial antiretroviral (ARV) regimens used by most national treatment programs in resource-limited settings include 2 nucleoside reverse-transcriptase inhibitors (NRTIs) and 1 non-nucleoside reverse-transcriptase inhibitor (NNRTI). The NRTIs in these regimens have consisted of zidovudine (AZT) or stavudine (d4T) with lamivudine (3TC); the NNRTI component has been nevirapine (NVP) or efavirenz (EFV). The 4 regimens created from these ARVs have saved hundreds of thousands of lives and provided hope to millions of others.

However, d4T mitochondrial toxicities and AZT anemia have cast a pall on the promise of ARV therapy. Therefore, the 2010 World Health Organization (WHO) ARV Treatment guidelines recommend phasing out d4T and adding 4 new options for first-line therapy: tenofovir (TDF)/3TC/NVP, TDF/emtricitabine (FTC)/NVP, TDF/3TC/EFV, and TDF/FTC/EFV. TDF is more potent and less toxic than AZT and d4T; median decreases in plasma human immunodeficiency virus (HIV)-1 RNA levels (virus load; VL) in subjects receiving TDF, AZT, or d4T monotherapy are 1.4, 0.5, and 0.5 $\log_{10}$, respectively [1].

It is not known, however, whether the 4 WHO-recommended, TDF-containing regimens are equally efficacious or even whether each offers an improvement over the older dual NRTI/NNRTI regimens. Thus, we performed a systematic review of the virological efficacy of the 4 WHO-recommended, TDF-containing regimens.

## METHODS

### Search Strategy

To identify studies assessing the efficacy of WHO-recommended, TDF-containing first-line ARV regimens, we searched for English-language papers and meeting abstracts that included prospective or retrospective studies of TDF/3TC/NVP, TDF/FTC/NVP, TDF/3TC/EFV, and TDF/FTC/EFV. Searches were conducted on 1 August 2011. We excluded studies (1) containing ARV-experienced patients; (2) lacking virological efficacy results; (3) containing multiple regimens for which the number of individuals receiving each regimen was unknown; and (4) containing 10 or fewer TDF-treated subjects (Figure 1). Both comparative and noncomparative studies were included in our search. The search strings and methods for identifying and reviewing studies are described in the Supplementary text.

### Data Analysis

Unless otherwise stated, standard drug dosages were used in the studies: (1) TDF 300 mg once daily; (2) AZT 300 mg twice daily; (3) d4T 30 or 40 mg twice daily; (4) 3TC 150 mg twice daily or 300 mg once daily; (5) FTC 200 mg once daily; (6) NVP 200 mg once daily for a 2-week lead-in period and then as 200 mg twice daily; and (7) EFV 600 mg once daily.

Treatment and virological failure were generally defined according to each study's criteria. Treatment failure was usually defined as failure to meet a prespecified level of virological suppression, regardless of whether the cause was study dropout, death, nonadherence, or drug toxicity. Virological failure was usually defined as treatment failure due to virologic nonresponse or rebound.

Genotypic drug resistance was defined as the emergence of a mutation known to reduce ARV susceptibility including (1) NNRTI-resistance mutations; (2) M184V, which primarily decreases susceptibility to 3TC and FTC; (3) K65R, which decreases susceptibility to each of the NRTIs except AZT; and (4) thymidine analog mutations, which decrease susceptibility to AZT and d4T, and, to a lesser degree, TDF, didanosine, and abacavir. Because K65R is the most important TDF-resistance mutation, we emphasized this mutation in the text.

For studies meeting inclusion criteria, we extracted study design, number of subjects, baseline median CD4 and VL, protocol-defined treatment and virological failure, and drug resistance data if available. For the comparative studies, we computed the relative risks (RRs) and 95% confidence intervals (CIs) for treatment and virological failure of the TDF-containing regimen versus its comparator regimen. Significance was determined using 2-tailed Fisher's exact test.

For studies in which additional data were needed, study authors were contacted. For example, the authors of the Nigerian PEPFAR cohort abstracts initially aggregated patients receiving TDF/3TC/NVP and TDF/FTC/NVP [2, 3]. Upon our request, the authors agreed to re-analyze the data so that patients receiving TDF/3TC/NVP and TDF/FTC/NVP were presented separately. Treatment failures included patients with virological failure, death, lost to follow-up, transfer, withdrawal, or medication switch without viral load support. Patients who switched between 3TC and FTC were excluded from analysis.

## RESULTS

Our literature search yielded 363 publications and 1427 conference abstracts. In a preliminary screen, 206 publications were identified and read to determine whether they met study inclusion criteria (Figure 1). Of these, 34 publications met study criteria: TDF/3TC/NVP (3 studies), TDF/FTC/NVP (9 studies), TDF/3TC/EFV (6 studies), and TDF/FTC/EFV (19 studies). Three studies contained more than one of these regimens [2, 3, 4, 5], and 1 study was described in 2 separate abstracts [2, 3].

Tables 1–4 summarize the study designs, subject characteristics, and outcome measures for each of the studies. Figure 2 displays the RR and 95% CI of treatment and virological failure for the comparative studies. Studies containing comparisons between a TDF-containing regimen and regimens containing non–US Food and Drug Administration (FDA)–approved ARVs or ARV combinations that have never been recommended by the US Department of Health and Human Services (DHHS) or WHO are shown in Tables 1–4, but not Figure 2. The following section reviews the main findings for each of the 4 regimens.

### TDF/3TC/NVP

The efficacy of TDF/3TC/NVP for initial ARV therapy was assessed in 3 studies (Table 1): (1) the DAUFIN trial, an open-label randomized controlled trial (RCT) of 71 subjects receiving TDF/3TC/NVP once daily or AZT/3TC/NVP twice daily [6]; (2) a retrospective PEPFAR cohort study of Nigerian patients receiving first-line ART including TDF/3TC/NVP (n = 285), TDF/FTC/NVP (n = 1852), TDF/FTC/EFV (n = 1330), and AZT/3TC/NVP (n = 5925) [2, 3]; and (3) a pilot trial of TDF/3TC/NVP once daily in 23 US subjects [7].

The DAUFIN trial was prematurely terminated because by week 12, significantly more subjects receiving TDF/3TC/NVP experienced virological failure (9 of 36; 25%) than subjects receiving AZT/3TC/NVP (1 of 35; 3%; P = .01) [6]. Moreover, 8 of 9 TDF/3TC/NVP recipients with virological failure developed NRTI and NNRTI resistance mutations, including 6 with K65R. No baseline characteristics appeared to explain the differences in outcomes between the 2 treatment arms.

The Nigerian PEPFAR cohort study compared virological outcomes of the ARV regimens administered in 4 clinics between 2006 and 2007 [2, 3]. Virological failure was significantly
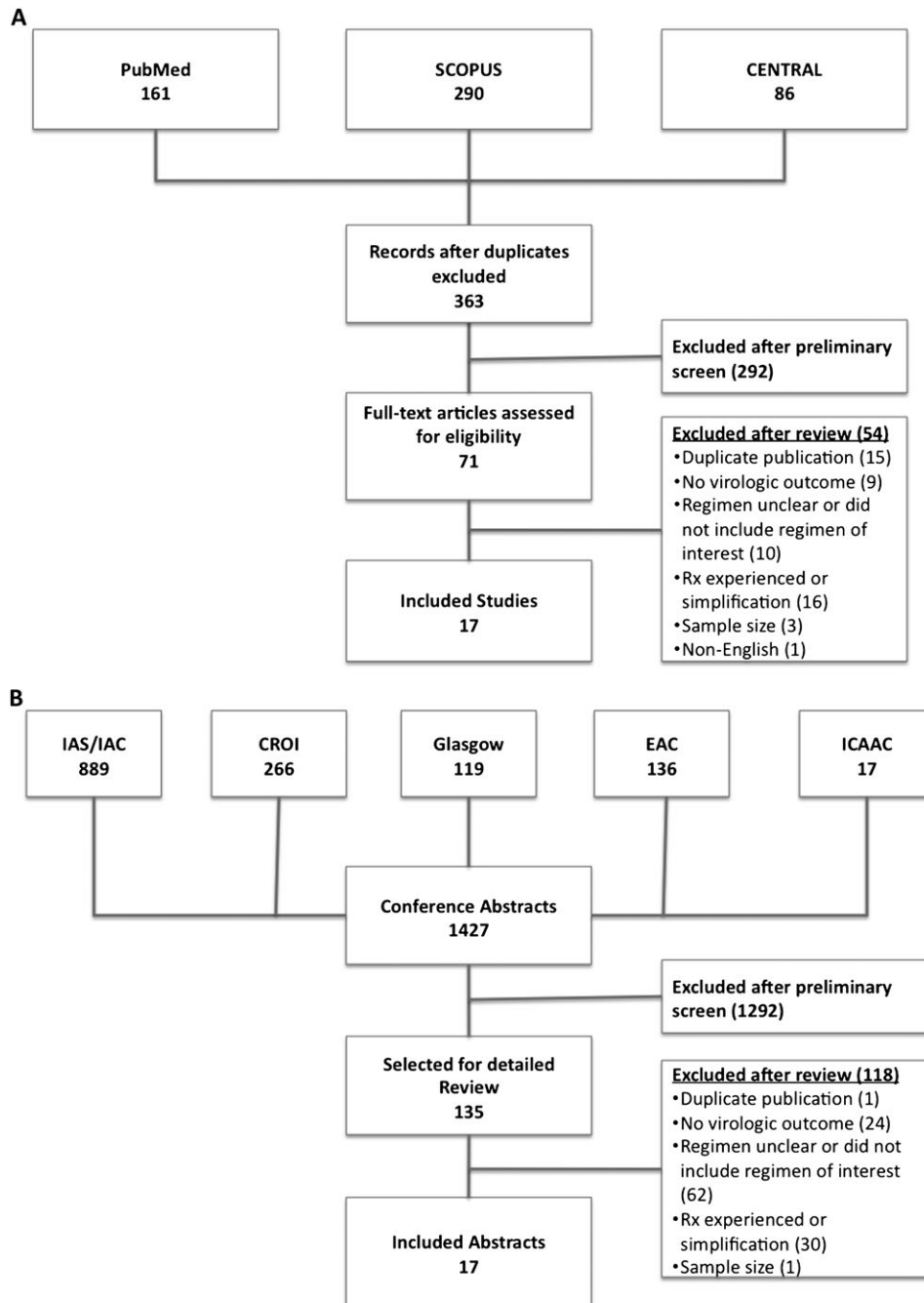
**Figure 1.** Summary of search results. *A*, Search results from online journal and trial databases; *B*, search results from conference abstracts. A description of the online databases and conferences can be found in the Supplementary Material. Definitions: ''Duplicate publication'': Multiple publications arising from the same study or patient cohort. ''No virologic outcome'': No virologic endpoints were available in the publication or abstract. ''Regimen or unclear or did not include regimen of interest'': Incomplete description of which antiretroviral (ARV) regimens were used, or failure to correlate specific ARV regimens with virologic data. ''Rx experienced or simplification'': Study subjects were either (1) treatment experienced, (2) included a mix of treatment naive and treatment experienced patients, or (3) virologically suppressed at baseline and received a tenofovir (TDF)-regimen as simplification. ''Sample size'': Study included 10 or fewer patients. ''Non-English'': Study was only published in a foreign language.

more common in patients receiving TDF/3TC/NVP (22 of 103; 21%) compared with AZT/3TC/NVP (207 of 2174; 10%, $P < .001$) and TDF/FTC/EFV (40 of 386; 10%, $P < .001$) but not with TDF/FTC/NVP (104 of 646; 16%, $P = .20$). Although baseline CD4 and VL were similar among TDF and AZT recipients, patients with anemia or hepatitis B were more likely to receive a TDF-containing regimen. The similar virological efficacies of TDF/FTC/EFV, AZT/3TC/NVP (and AZT/3TC/EFV)

**Table 1. Studies of Tenofovir/Lamivudine/Nevirapine for Initial Antiretroviral Therapy**

| Reference[a] | Study Design (VL Endpoint) | Regimen | No. | CD4 | VL | Weeks | Rx Failure[b] | VF[c] | VF P Value[d] | Genotypic Resistance Testing |
|---|---|---|---|---|---|---|---|---|---|---|
| DAUFIN [6] | Prospective OL randomized trial (VL >2 log$_{10}$ ↓ by wk 12 and <400 through wk 96) | TDF/3TC/NVP (QD) | 36 | 191 | 5.0 | 12 | 15 (42%) | 9 (25%) | | Prematurely terminated by wk 12. Eight subjects with VF on TDF/3TC/NVP got GRT. All developed NRTI + NNRTI DRMs including 6 with 65R. The AZT/3TC/NVP subject had no DRMs. |
| | | AZT/3TC/NVP (BID) | 35 | 195 | 4.9 | 12 | 11 (31%) | 1 (3%) | .01 | |
| Nigerian PEPFAR [2, 3] | Retrospective cohort study (VL <1000 at wk 24) | TDF/3TC/NVP (BID) | 285 | 132 | 4.6 | 48 | 126 (44%) | 22/103 (21%) | | NA |
| | | TDF/FTC/NVP (BID) | 1852 | 137 | 4.7 | 48 | 761 (41%) | 104/646 (16%) | .20 | |
| | | TDF/FTC/EFV | 1330 | 136 | 4.7 | 48 | 552 (41%) | 40/386 (10%) | .005 | |
| | | AZT/3TC/NVP (BID) | 5925 | 147 | 4.6 | 48 | 1998 (34%) | 207/2174 (10%) | <.001 | |
| Boehringer-Ingelheim [7] | Prospective OL pilot trial (VL <75 at wk 24) | TDF/3TC/NVP (QD) | 23 | 169 | 5.2 | 24 | 13 (57%) | 7 (30%) | — | Prematurely terminated because of the high rate of VF, which occurred in 7 of 8 subjects with baseline VL ≥100 000. The 7 subjects with VF had NRTI ± NNRTI DRMs. 65R occurred in 1 subject. |

Abbreviations: AZT, zidovudine; BID, twice daily; CD4, CD4+ cells/mm$^3$; DRMs, drug resistance mutations; FTC, emtricitabine; GRT, genotypic resistance testing; NA, not available; NNRTI, non-nucleoside reverse-transcriptase inhibitor; NRTI, nucleoside reverse-transcriptase inhibitor; NVP, nevirapine; OL, open-labeled; QD, once daily; TDF, tenofovir; VL, virus load in RNA log$_{10}$ copies/ml; wk, week; 3TC, lamivudine.

[a] Reference: The Nigerian PEPFAR study results are also presented in Tables 2 and 4.

[b] Rx Failure: Treatment failure defined as the proportion of subjects failing to achieve virological success according to the authors' intention-to-treat analysis. For the Nigerian PEPFAR study, patients with missing data were excluded from this analysis.

[c] VF: Virological failure defined as treatment failure due to virologic nonresponse or rebound. VF calculated as (number of subjects with VF)/(total number of subjects), unless the authors used a different definition (in which case authors' numbers are shown).

[d] VF P value: P values comparing virological failure in TDF/3TC/NVP vs comparator arm.

**Table 2. Studies of Tenofovir/Emtricitabine/Nevirapine for Initial Antiretroviral Therapy**

| Reference[a] | Study Design (VL Endpoint) | Regimen | No. | CD4 | VL | Weeks | Rx Failure[b] | VF[c] | VF P Value[d] | Genotypic Resistance Testing |
|---|---|---|---|---|---|---|---|---|---|---|
| Brescia University [8] | Prospective randomized trial (VL↓ 1log by wk 12) | TDF/FTC/NVP (BID) | 7 | 132 | 5.1 | 12 | 5 (71%) | 3 (42%) | | 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%) | .19 | |
| ARTEN [9] | 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%) | | 29 of 44 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%) | .35 | |
| NEWART [10] | Prospective OL randomized trial (VL<50 at wk 48) | TDF/FTC/NVP (BID) | 75 | 176 | 4.9 | 48 | 29 (39%) | 11 (15%) | | 7of 9 NVP subjects with GRT had NRTI ± NNRTI DRMs, including 5 with ''reduced response'' to TDF. 0 of 9 ATV/r subjects with GRT had DRMs. |
| | | TDF/FTC/ATVr (QD) | 77 | 193 | 4.9 | 48 | 27 (35%) | 12 (16%) | >.5 | |
| VERxVE [11] | Prospective randomized trial (VL<50 at wk 48) | TDF/FTC/NVP IR (BID) | 506 | 227 | 4.7 | 48 | 122 (24%) | 30 (6%) | | 31 of 54 NVP IR subjects with GRT had NRTI ± NNRTI DRMs including 7 with 65R. 19 of 32 NVP XR subjects had NRTI ± NNRTI DRMs including 7 with 65R |
| | | TDF/FTC/NVP XR (QD) | 505 | 229 | 4.7 | 48 | 96 (19%) | 16 (3%) | .05 | |
| OCTANE Trial 2 [12] | Prospective OL randomized trial (VL <400 at wk 24) | TDF/FTC/NVP (BID) | 249 | 121 | 5.2 | 72 | 34 (14%) | 29 (12%) | | NA |
| | | TDF/FTC/LPVr (BID) | 251 | 121 | 5.2 | 72 | 36 (14%) | 32 (13%) | >.5 | |
| DAYANA [4] | Prospective OL randomized trial (VL<50 at wk 48) | TDF/FTC/NVP (BID) | 31 | 200 | 5.4 | 48 | 7 (23%) | 3/27 (11%) | | No subjects with VF in the TDF/FTC/NVP and TDF/FTC/EFV arms had DRMs. 3 of 6 subjects with VF in TDF/LPV/r arm had PI DRMs. 1 of 3 subjects with VF in TDF/FTC/AZT arm had 184V and TAMS |
| | | TDF/FTC/EFV (QD) | 30 | 200 | 5.4 | 48 | 7 (30%) | 3/25 (12%) | >.5 | |
| | | TDF/LPV/r (QD) | 29 | 200 | 5.4 | 48 | 12 (59%) | 6/18 (33%) | .13 | |
| | | TDF/FTC/AZT | 29 | 200 | 5.4 | 48 | 5 (17%) | 3/27 (11%) | >.5 | |
| Nigerian PEPFAR [2, 3] | Retrospective cohort study (VL <1000 at wk 24) | TDF/FTC/NVP (BID) | 1852 | 137 | 4.7 | 48 | 761 (41%) | 104/646 (16%) | | NA |
| | | TDF/3TC/NVP (BID) | 285 | 132 | 4.6 | 48 | 126 (44%) | 22/103 (21%) | .20 | |
| | | TDF/FTC/EFV | 1330 | 136 | 4.7 | 48 | 552/1330 (41%) | 40/386 (10%) | .01 | |
| | | AZT/3TC/NVP (BID) | 5925 | 146 | 4.6 | 48 | 1998 (34%) | 207/2174 (10%) | <.001 | |
| Frankfurt Cohort [5] | Retrospective cohort study (VL<50 at wk 48) | TDF/FTC/NVP (BID) | 72 | 201 | 4.8 | 48 | 23 (32%) | 10 (13%) | | NA |
| | | TDF/FTC/EFV | 77 | 208 | 5.1 | 48 | 16 (21%) | 6 (8%) | .29 | |

**Table 2 continued.**

| Reference[a] | Study Design (VL Endpoint) | Regimen | No. | CD4 | VL | Weeks | Rx Failure[b] | VF[c] | VF P Value[d] | Genotypic Resistance Testing |
|---|---|---|---|---|---|---|---|---|---|---|
| Nevada Group [13] | Retrospective cohort study (VL <50 at wk 48) | TDF/FTC/NVP (BID) | 123 | 215 | 4.8 | 48 | 27 (22%) | 8 (7%) | — | In 8 subjects with VF, 6 had 184V, 5 had ≥1 NNRTI DRM, and 3 had 65R. |

Abbreviations: ATVr, ritonavir-boosted atazanavir; AZT, zidovudine; BID, twice daily; CD4, CD4+ cells/mm³; DRMs, drug resistance mutations; EFV, efavirenz; FTC, emtricitabine; GRT, genotypic resistance testing; IR, intermediate release; LPVr, ritonavir-boosted lopinavir; NA, not available; NNRTI, non-nucleoside reverse-transcriptase inhibitor; NRTI, nucleoside reverse-transcriptase inhibitor; NVP, nevirapine; OL, open-labeled; QD, once daily; TDF, tenofovir; VL, virus load in RNA log$_{10}$ copies/ml; wk, week; XR, extended release; 3TC, lamivudine.

[a] Reference: The DAYANA and Frankfurt Cohort studies also appear in Table 4. The Nigerian PEPFAR study also appears in Tables 1 and 4.

[b] Rx Failure: Treatment failure defined as proportion of subjects failing to achieve virological success according to the authors' intention-to-treat analysis. In the Nigerian PEPFAR study, patients with missing data were excluded from analysis of Rx Failure.

[c] VF: Virological failure defined as treatment failure due to virologic nonresponse or rebound. VF calculated as (number of subjects with VF)/(total number of subjects), unless the authors used a different definition (in which case authors' numbers are shown). For the ARTEN study, VF includes subjects who discontinued the study medication due to investigator-defined lack of efficacy and were not included in the protocol's on-study analysis.

[d] VF P value: P values comparing virological failure in TDF/FTC/NVP vs comparator arm.

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in the PEPFAR cohort [3] suggests that the decreased virological efficacy of TDF/3TC/NVP and TDF/FTC/NVP versus the AZT regimens is less likely to be due to sicker patients receiving TDF.

In the TDF/3TC/NVP pilot trial, 7 of 23 subjects (30%) developed virological failure, including 5 with NRTI and/or NNRTI resistance [7]. Like the DAUFIN trial, this trial was prematurely terminated because of frequent early virological failure.

Among the 15 subjects receiving TDF/3TC/NVP who underwent genotypic resistance testing, 7 (47%) developed K65R.

**TDF/FTC/NVP**

The efficacy of TDF/FTC/NVP for initial ARV therapy was assessed in 9 studies (Table 2). Five prospective [4, 8–10, 12] and 2 retrospective studies [2, 5] compared TDF/FTC/NVP to another regimen. An 8th prospective study compared the recently FDA-approved extended-release (XR) form of NVP with standard NVP in combination with TDF/FTC [11]. There was also a single-arm retrospective study of TDF/FTC/NVP [13].

Three large comparative trials reported that the virological efficacy of TDF/FTC/NVP was similar to that of TDF/FTC plus ATV/r (ARTEN [9] and NEWART [10]) or LPV/r (OCTANE Trial 2) [12] (Figure 2). However, in the ARTEN and OCTANE trials, significantly more subjects discontinued the NVP arm than the boosted-protease inhibitor (PI) arm.

In contrast, TDF/FTC/NVP was less efficacious than AZT/3TC/NVP and TDF/FTC/EFV in the Nigerian PEPFAR cohort [2, 3]. In addition, a small RCT was terminated prematurely because 3 of 7 (42%) subjects receiving TDF/FTC plus NVP twice daily had early virological failure and resistance compared with 0 of 7 receiving TDF/FTC/ATV/r once daily (P = .2) [8]. The VERxVE trial demonstrated a small increased risk of virological failure with TDF/FTC/NVP twice daily (30 of 506; 6%) compared with TDF/FTC/NVP XR once daily (16 of 505; 3%; P = .05) [11]. Fifty-five subjects discontinued the study during the NVP lead-in phase and were not included in the randomization.

Among 112 subjects receiving TDF/FTC/NVP who underwent genotypic resistance testing, 23 (21%) developed the NRTI-resistance mutation K65R (Table 2).

**TDF/3TC/EFV**

The efficacy of TDF/3TC/EFV for initial ARV therapy was assessed in 5 RCTs [14–16, 18, 19] and 1 retrospective cohort [17]. In the comparative studies, there were no statistically significant differences between TDF/3TC/EFV and its comparator arms, which included d4T/3TC/EFV, ddI/3TC/EFV, AZT/3TC/EFV, TDF/3TC/RAL, and AZT/3TC/LPV/r (Figure 2) [15–19]. Among 63 subjects receiving TDF/3TC/EFV who underwent genotypic resistance testing, 16 (25%) developed K65R (Table 3).

**Table 3. Studies of Tenofovir/Lamivudine/Efavirenz for Initial Antiretroviral Therapy**

| Reference | Study Design (VL Endpoint) | Regimen | No. | CD4 | VL | Weeks | Rx Failure[a] | VF[b] | VF P Value[c] | Genotypic Resistance Testing |
|---|---|---|---|---|---|---|---|---|---|---|
| GS-903 [14] | Prospective randomized trial (VL <400 at wk 48) | TDF/3TC/EFV | 299 | 276 | 4.9 | 48 | 60 (20%) | 29 (10%) | | Of 29 TDF subjects with GRT, 16 had ≥1 NNRTI DRM, 12 had 184V, and 7 had 65R. Of 25 d4T subjects with GRT, 12 had ≥1 NNRTI DRM, 8 had 184V, 2 had 65R |
| | | d4T/3TC/EFV | 301 | 283 | 4.9 | 48 | 48 (16%) | 25 (8%) | >.5 | |
| Merck-004 [15] | Prospective randomized trial (VL <50 at wk 48) | TDF/3TC/EFV | 38 | 280 | 4.8 | 48 | 5 (13%) | 1 (3%) | | The EFV subject with GRT had ≥1 NNRTI DRM, 184V, 65R. Two RAL subjects with GRT had ≥1 RAL DRM and 184V. |
| | | TDF/3TC/RAL (BID) | 160 | 305 | 4.8 | 48 | 23 (14%) | 5 (3%) | >.5 | |
| TEDAL [16] | Prospective randomized trial (VL <50 at wk 48) | TDF/3TC/EFV | 64 | 203 | 5.3 | 48 | 21 (33%) | 8 (13%) | | All 27 subjects with VF had NRTI and/or NNRTI DRMS. 5 TDF/3TC/EFV subjects had 65R |
| | | DDI/3TC/EFV | 72 | 172 | 5.4 | 48 | 19 (26%) | 6 (8%) | >.5 | |
| | | DDI/ABC/EFV | 63 | 183 | 5.3 | 48 | 29 (46%) | 13 (21%) | .24 | |
| Parkland [17] | Retrospective cohort study (VL <400 at wk 48) | TDF/3TC/EFV | 163 | NA | 4.8 | 48 | NA | 28 (17%) | | NA |
| | | AZT/3TC/EFV | 313 | NA | 4.5 | 48 | NA | 56 (18%) | >.5 | |
| SISTHER Substudy [18] | Prospective randomized trial (VL <50 at wk 52) | TDF/3TC/EFV | 83 | 194 | 5.3 | 28 | 26 (30%) | NA | | 2 of 5 subjects TDF/3TC/EFV 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 | >.5 | |
| Elvucitabine Phase II trial [19] | Prospective randomized trial (VL <50 at wk 48) | TDF/3TC/EFV | 37 | 325 | 4.8 | 96 | 8 (22%) | 1/30 (3%) | | 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%) | >.5 | |

Abbreviations: AZT, zidovudine; BID, twice daily; CD4, CD4+ cells/mm$^3$; d4T, stavudine; DDI, didanosine; DRMs, drug resistance mutations; EFV, efavirenz; ELV, elvucitabine (an investigational NRTI); GRT, genotypic resistance testing; LPVr, ritonavir-boosted lopinavir; NA, not available; NNRTI, non-nucleoside reverse-transcriptase inhibitor; NRTI, nucleoside reverse-transcriptase inhibitor; QD, once daily; RAL, raltegravir; TDF, tenofovir; VL, virus load in RNA log$_{10}$ copies/ml; wk, week; 3TC, lamivudine.

[a] Rx Failure: Treatment failure defined as proportion of subjects failing to achieve virological success according to the authors' intention-to-treat analysis.

[b] VF: Virological failure defined as treatment failure due to virologic nonresponse or rebound. VF calculated as (number of subjects with VF)/(total number of subjects), unless the authors used a different definition (in which case authors' numbers are shown).

[c] VF P value: P values comparing virological failure in TDF/3TC/EFV vs comparator arm. If no VF results are available, P value for Rx Failure is given.

**Table 4. Studies of Tenofovir/Emtricitabine/Efavirenz for Initial Antiretroviral Therapy**

| Reference[a] | Study Design (VL Endpoint) | Regimen[b] | No. | CD4 | VL | Weeks | Rx Failure[b] | VF[c] | VF P Value[d] | Genotypic Resistance Testing |
|---|---|---|---|---|---|---|---|---|---|---|
| GS-934 [20] | Prospective randomized trial (VL <400 at wk 48) | TDF/FTC/EFV | 244 | 233 | 5.0 | 48 | 38 (16%) | 12 (5%) | | 9 of 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%) | .06 | |
| STARTMRK [21] | Prospective randomized trial (VL <50 at wk 48) | TDF/FTC/EFV | 282 | 217 | 5.0 | 48 | 52 (18%) | 39 (14%) | | 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%) | .15 | |
| ACTG 5202 [22] | Prospective randomized trial (VL <200 at wk 24) | TDF/FTC/EFV | 464 | 234 | 4.7 | 48 | 97 (21%) | 57 (12%) | | Of 57 subjects with VF on TDF/FTC/EFV, 27 had NNRTI DRMs, 5 had 184V and 4 had 65R. Of the 72 subjects with VF on ABC/3TC/EFV, 41 had NNRTI DRMs, 22 had 184V and 3 had 65R. Of the 57 subjects with VF on TDF/FTC/ATV/r, 5 had NNRTI DRMs. Of 83 subjects on ABC/3TC/ATV/r, 11 had 184V |
| | | ABC/3TC/EFV | 465 | 225 | 4.7 | 48 | 132 (28%) | 72 (15%) | .16 | |
| | | TDF/FTC/ATV/r | 465 | 224 | 4.7 | 48 | 101 (23%) | 57 (12%) | >.5 | |
| | | ABC/3TC/ATV/r | 463 | 236 | 3.6 | 48 | 125 (27%) | 83 (18%) | .02 | |
| ASSERT [23] | Prospective randomized trial (VL <50 at wk 48) | TDF/FTC/EFV | 193 | 230 | 5.1 | 48 | 56 (29%) | 2 (1%) | | 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%) | .17 | |
| ALTAIR [24] | Prospective randomized trial (VL <50 at wk 48) | TDF/FTC/EFV | 114 | 227 | 4.7 | 48 | 17 (10%) | 4 (4%) | | Of 4 subjects with VF on TDF/FTC/EFV, 1 had NNRTI and 1 had 184V DRMs. Of 11 subjects with VF on TDF/FTC/AZT/ABC, 2 had DRMs, including 1 with 65R and 1 with 184V + a TAM. Of 4 subjects with VF on TDF/FTC/ATV/r 1 had 184V |
| | | TDF/FTC/ATV/r | 105 | 235 | 4.8 | 48 | 12 (8%) | 4 (4%) | >.5 | |
| | | TDF/FTC/AZT/ABC | 103 | 226 | 4.6 | 48 | 28 (24%) | 11 (11%) | .06 | |
| ACTG 5175 (PEARLS) [25] | Prospective randomized trial (VL <400 at wk 48) | TDF/FTC/EFV | 526 | 162 | 5.0 | 48 | 68 (13%) | NA | | NA |
| | | AZT/3TC/EFV | 519 | 169 | 5.1 | 48 | 78 (15%) | NA | >.5 | |
| DAYANA [4] | Prospective OL randomized trial (VL <50 at wk 48) | TDF/FTC/EFV (QD) | 30 | 200 | 5.4 | 48 | 7 (30%) | 3/25 (12%) | | No subjects with VF in the TDF/FTC/NVP and TDF/FTC/EFV arms had DRMs. 3 of 6 subjects with VF in TDF/LPV/r arm had PI DRMs. 1 of 3 subjects with VF in TDF/FTC/AZT arm had 184V and TAMS |
| | | TDF/FTC/NVP (BID) | 31 | 200 | 5.4 | 48 | 7 (23%) | 3/27 (11%) | >.5 | |

*Table 4 continued.*

| Reference[a] | Study Design (VL Endpoint) | Regimen[b] | No. | CD4 | VL | Weeks | Rx Failure[b] | VF[c] | VF P Value[d] | Genotypic Resistance Testing |
|---|---|---|---|---|---|---|---|---|---|---|
| | | TDF/LPV/r (QD) | 29 | 200 | 5.4 | 48 | 12 (59%) | 6/18 (33%) | .13 | |
| | | TDF/FTC/AZT | 29 | 200 | 5.4 | 48 | 5 (17%) | 3/27 (11%) | >.5 | |
| Advanz-3 [26] | Prospective OL randomized trial (VL <50 at wk 48) | TDF/FTC/EFV | 28 | 48 | 5.1 | 48 | 7 (25%) | 4 (14%) | | NA |
| | | TDF/FTC/ATV/r | 30 | 32 | 5.5 | 48 | 8 (27%) | 1 (3%) | .19 | |
| | | TDF/FTC/LPV/r | 29 | 30 | 5.1 | 48 | 13 (45%) | 4 (14%) | >.5 | |
| ECHO [27] | Prospective randomized trial (VL <50 at wk 48) | TDF/FTC/EFV | 344 | 257 | 5.0 | 48 | 59 (17%) | 19 (6%) | | Of 19 subjects with VF on TDF/FTC/EFV, 8 had NNRTI and 4 had 184V. Of 45 subjects with VF on TDF/FTC/TMC278, 26 had NNRTI, 26 had 184V and 3 had K65R DRMs |
| | | TDF/FTC/RPV | 346 | 240 | 5.0 | 48 | 59 (17%) | 45 (13%) | .001 | |
| QUAD Study [28] | Prospective randomized trial (VL <50 at wk 48) | TDF/FTC/EFV | 23 | 436 | 4.58 | 48 | 1 (5%) | 0 | | No genotypic resistance reported |
| | | EVG/COBI/TDF/FTC | 48 | 354 | 4.59 | 48 | 2 (4%) | 0 | >.5 | |
| Lersiverine Phase IIb [29] | Prospective randomized trial (VL <50 at wk 48) | TDF/FTC/EFV | 63 | 310 | 4.7 | 48 | 9 (14%) | 1 (2%) | | The subject with VF receiving EFV had K103N. 4 of 9 LRV subjects had other NNRTI DRMs |
| | | TDF/FTC/LRV 500 mg | 65 | 310 | 4.7 | 48 | 14 (21%) | 5 (8%) | .21 | |
| | | TDF/FTC/LRV 750 mg | 65 | 310 | 4.7 | 48 | 14 (21%) | 4 (6%) | .37 | |
| CCTG 589 [30] | Prospective OL pilot trial (VL <50 at wk 48) | TDF/FTC/EFV | 25 | 296 | 4.7 | 48 | 7 (28%) | 3 (12%) | | NA |
| | | RAL/LPV/r | 26 | 369 | 4.7 | 48 | 12 (46%) | 3 (12%) | >.5 | |
| Acute HIV [31] | Prospective single arm trial (VL <50 at wk 48) | TDF/FTC/EFV | 61 | 541 | 5.2 | 48 | 6/41 (15%) | 1/41 (2%) | — | NA |
| Nigerian PEPFAR[d] [2, 3] | Retrospective cohort study (VL <1000 at week 24, confirmed by wk 48) | TDF/FTC/EFV | 1330 | 136 | 4.7 | 48 | 552/1330 (41%) | 40/386 (10%) | | NA |
| | | TDF/3TC/NVP (BID) | 285 | 132 | 4.6 | 48 | 126 (44%) | 22/103 (21%) | .005 | |
| | | TDF/FTC/NVP (BID) | 1852 | 137 | 4.7 | 48 | 761 (41%) | 104/646 (16%) | .01 | |
| | | AZT/3TC/NVP (BID) | 5925 | 147 | 4.6 | 48 | 1998 (34%) | 207/2174 (10%) | >.5 | |
| ANRS Senegal [32] | Prospective pilot trial (VL <50 at wk 48) | TDF/FTC/EFV | 40 | 111 | 5.3 | 48 | 11(28%) | 7 (17%) | — | NA |
| Frankfurt Cohort[a] [5] | Retrospective cohort study (VL <50 at wk 48) | TDF/FTC/EFV (QD) | 77 | 208 | 5.1 | 48 | 16 (21%) | 6 (8%) | | NA |
| | | TDF/FTC/NVP (BID) | 72 | 201 | 4.8 | 48 | 23 (32%) | 10 (13%) | .29 | |

Table 4 continued.

| Reference[a] | Study Design (VL Endpoint) | Regimen[b] | No. | CD4 | VL | Weeks | Rx Failure[b] | VF[c] | VF P Value[d] | Genotypic Resistance Testing |
|---|---|---|---|---|---|---|---|---|---|---|
| TOKEN Study [33] | Retrospective cohort study (VL <40 at wk 48) | TDF/FTC/EFV | 81 | 172 | 5.4 | 48 | 14 (17%) | NA | | NA |
| | | ABC/3TC/EFV | 58 | 172 | 5.4 | 48 | 9 (15%) | NA | >.5 | |
| Sydney Clinic [34] | Retrospective cohort study (undetectable VL at wk 48) | TDF/FTC/EFV | 17 | 237 | 5.0 | 48 | 4 (24%) | 4 (22%) | | NA |
| | | AZT/3TC/EFV | 14 | 175 | 4.7 | 48 | 3 (19%) | 2 (11%) | >.5 | |
| 1-pill vs 2-pill TDF/FTC/EFV [35] | Retrospective cohort study | TDF/FTC/EFV (1-pill) | 59 | 250 | 4.5 | 48 | 7 (12%) | NA | | NA |
| | | TDF/FTC/EFV (2-pills) | 79 | 244 | 4.5 | 48 | 4 (5%) | NA | .20 | |

Abbreviations: ABC, abacavir; ATV/r, ritonavir-boosted atazanavir; AZT, zidovudine; BID, twice daily; COBI, cobicistat; CD4, CD4+ cells/mm³; d4T, stavudine; DRMs, drug resistance mutations; EFV, efavirenz; EVG, elvitegravir; LPV/r, ritonavir-boosted lopinavir; LRV, lersiverine; NA, not available; NNRTI, non-nucleoside reverse-transcriptase inhibitor; NRTI, nucleoside reverse-transcriptase inhibitor; NVP, nevirapine; OL, open-labeled; QD, once daily; RAL, raltegravir; RPV, rilpivirine; TDF, tenofovir; TMC 278, rilpivirine; VL, virus load in RNA log₁₀ copies/ml; wk, week; 3TC, lamivudine.

a Reference: The DAYANA and Frankfurt Cohort studies also appear in Table 2. The Nigerian PEPFAR study also appears in Tables 1 and 2.

b Rx Failure: Treatment failure defined as proportion of subjects failing to achieve virological success according to the authors' intention-to-treat analysis.

c VF: Virological failure defined as treatment failure due to virologic nonresponse or rebound. VF calculated as (number of subjects with VF)/(total number of subjects), unless the authors used a different definition (in which case authors' numbers are shown).

d VF P value: P values comparing virological failure in TDF/FTC/EFV versus comparator arm. If no VF results are available, P value for Rx Failure is given.

## TDF/FTC/EFV

The efficacy of TDF/FTC/EFV was assessed in 12 prospective trials [4, 20–29, 31], 5 retrospective studies [3, 5, 33–35], and 2 pilot trials [30, 32]. In 4 comparative studies, TDF/FTC/EFV was associated with decreased virological failure compared with 1 or more of its comparator arms (Figure 2). In the phase III GS-934 trial, TDF/FTC/EFV demonstrated a trend towards decreased virological failure compared with AZT/3TC/EFV having an RR = 0.5 (95% CI, .3–1.0; $P$ = .06). In the phase III ECHO trial, TDF/FTC/EFV was associated with significantly decreased virological failure compared with TDF/FTC/RPV having an RR = 0.4 (95% CI, .2–.7; $P$ = .001). In A5202, TDF/FTC/EFV was associated with significantly decreased virological failure compared with ABC/3TC/ATV/r. In the PEPFAR study, TDF/FTC/EFV was associated with significantly decreased virological failure compared with TDF/3TC/NVP and TDF/FTC/NVP but not AZT/3TC/NVP. In no study was TDF/FTC/EFV inferior to a comparator arm. Among 141 subjects receiving TDF/FTC/EFV who underwent genotypic resistance testing, 4 (3%) developed K65R.

## DISCUSSION

The 2009 DHHS ARV Treatment Guidelines (http://www.aidsinfo.nih.gov/guidelines/GuidelineDetail.aspx?GuidelineID=7&ClassID=1, last acccessed 1 August 2011) classify TDF/3TC/NVP and TDF/FTC/NVP as "regimens that may be acceptable but should be used with caution." Our study provides a comprehensive analysis that supports this recommendation and provides insight into the relative efficacies of each of the 4 WHO-recommended TDF-containing regimens.

TDF/3TC/NVP once daily was inferior to AZT/3TC/NVP in a small European RCT, which was prematurely terminated due to early virological failure [6]. A pilot trial of TDF/3TC/NVP once daily was also terminated prematurely because 7 of the first 23 participants experienced early virological failure and drug resistance [7]. The Nigerian PEPFAR study found an increased risk of virological failure with TDF/3TC/NVP twice daily in comparison with AZT/3TC/NVP and TDF/FTC/EFV [2, 3]. TDF/3TC/NVP is the least well-studied of the regimens, and to our knowledge there are no ongoing studies of this regimen (http://www.clinicaltrials.gov, last accessed 1 August 2011).

TDF/FTC/NVP appeared to be as efficacious as its comparator regimens in 4 of 7 studies [4, 9, 10, 12]. However, this regimen was inferior to AZT/3TC/NVP and TDF/FTC/EFV in the Nigerian PEPFAR study [2, 3] and to TDF/FTC/NVP XR in the VERxVE study [11]. In addition, increased early virological failure led to premature study discontinuation in a small prospective study [8]. In contrast, TDF/3TC/EFV and TDF/FTC/EFV were consistently as efficacious as their comparator regimens.
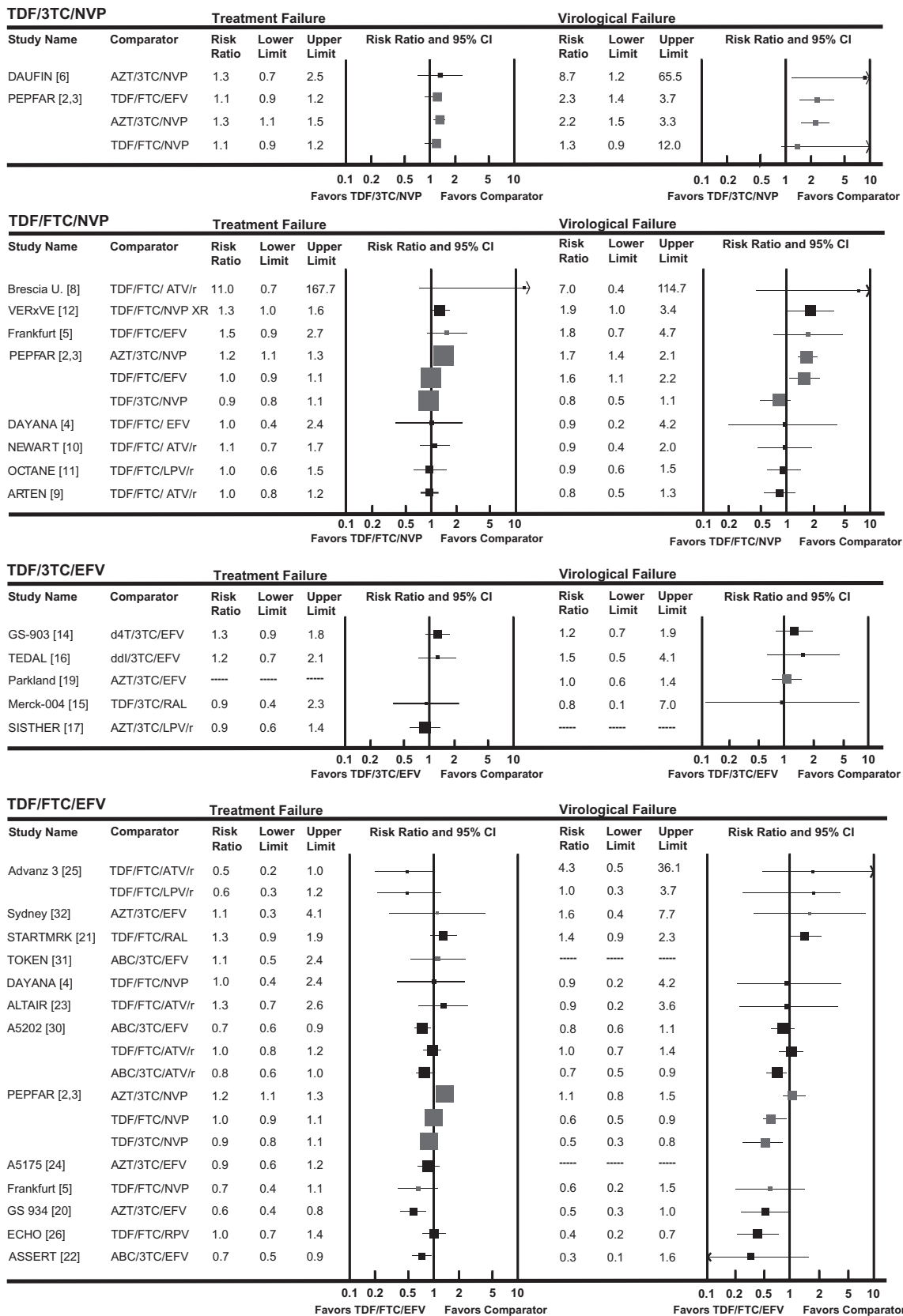
## TDF/3TC/NVP

**Treatment Failure**

| Study Name | Comparator | Risk Ratio | Lower Limit | Upper Limit | Risk Ratio and 95% CI |
|---|---|---|---|---|---|
| DAUFIN [6] | AZT/3TC/NVP | 1.3 | 0.7 | 2.5 | |
| PEPFAR [2,3] | TDF/FTC/EFV | 1.1 | 0.9 | 1.2 | |
| | AZT/3TC/NVP | 1.3 | 1.1 | 1.5 | |
| | TDF/FTC/NVP | 1.1 | 0.9 | 1.2 | |

**Virological Failure**

| Risk Ratio | Lower Limit | Upper Limit | Risk Ratio and 95% CI |
|---|---|---|---|
| 8.7 | 1.2 | 65.5 | |
| 2.3 | 1.4 | 3.7 | |
| 2.2 | 1.5 | 3.3 | |
| 1.3 | 0.9 | 12.0 | |

0.1 0.2 0.5 1 2 5 10  Favors TDF/3TC/NVP  Favors Comparator

## TDF/FTC/NVP

**Treatment Failure**

| Study Name | Comparator | Risk Ratio | Lower Limit | Upper Limit | Risk Ratio and 95% CI |
|---|---|---|---|---|---|
| Brescia U. [8] | TDF/FTC/ ATV/r | 11.0 | 0.7 | 167.7 | |
| VERxVE [12] | TDF/FTC/NVP XR | 1.3 | 1.0 | 1.6 | |
| Frankfurt [5] | TDF/FTC/EFV | 1.5 | 0.9 | 2.7 | |
| PEPFAR [2,3] | AZT/3TC/NVP | 1.2 | 1.1 | 1.3 | |
| | TDF/FTC/EFV | 1.0 | 0.9 | 1.1 | |
| | TDF/3TC/NVP | 0.9 | 0.8 | 1.1 | |
| DAYANA [4] | TDF/FTC/ EFV | 1.0 | 0.4 | 2.4 | |
| NEWART [10] | TDF/FTC/ ATV/r | 1.1 | 0.7 | 1.7 | |
| OCTANE [11] | TDF/FTC/LPV/r | 1.0 | 0.6 | 1.5 | |
| ARTEN [9] | TDF/FTC/ ATV/r | 1.0 | 0.8 | 1.2 | |

**Virological Failure**

| Risk Ratio | Lower Limit | Upper Limit | Risk Ratio and 95% CI |
|---|---|---|---|
| 7.0 | 0.4 | 114.7 | |
| 1.9 | 1.0 | 3.4 | |
| 1.8 | 0.7 | 4.7 | |
| 1.7 | 1.4 | 2.1 | |
| 1.6 | 1.1 | 2.2 | |
| 0.8 | 0.5 | 1.1 | |
| 0.9 | 0.2 | 4.2 | |
| 0.9 | 0.4 | 2.0 | |
| 0.9 | 0.6 | 1.5 | |
| 0.8 | 0.5 | 1.3 | |

0.1 0.2 0.5 1 2 5 10  Favors TDF/FTC/NVP  Favors Comparator

## TDF/3TC/EFV

**Treatment Failure**

| Study Name | Comparator | Risk Ratio | Lower Limit | Upper Limit | Risk Ratio and 95% CI |
|---|---|---|---|---|---|
| GS-903 [14] | d4T/3TC/EFV | 1.3 | 0.9 | 1.8 | |
| TEDAL [16] | ddI/3TC/EFV | 1.2 | 0.7 | 2.1 | |
| Parkland [19] | AZT/3TC/EFV | ----- | ----- | ----- | |
| Merck-004 [15] | TDF/3TC/RAL | 0.9 | 0.4 | 2.3 | |
| SISTHER [17] | AZT/3TC/LPV/r | 0.9 | 0.6 | 1.4 | |

**Virological Failure**

| Risk Ratio | Lower Limit | Upper Limit | Risk Ratio and 95% CI |
|---|---|---|---|
| 1.2 | 0.7 | 1.9 | |
| 1.5 | 0.5 | 4.1 | |
| 1.0 | 0.6 | 1.4 | |
| 0.8 | 0.1 | 7.0 | |
| ----- | ----- | ----- | |

0.1 0.2 0.5 1 2 5 10  Favors TDF/3TC/EFV  Favors Comparator

## TDF/FTC/EFV

**Treatment Failure**

| Study Name | Comparator | Risk Ratio | Lower Limit | Upper Limit | Risk Ratio and 95% CI |
|---|---|---|---|---|---|
| Advanz 3 [25] | TDF/FTC/ATV/r | 0.5 | 0.2 | 1.0 | |
| | TDF/FTC/LPV/r | 0.6 | 0.3 | 1.2 | |
| Sydney [32] | AZT/3TC/EFV | 1.1 | 0.3 | 4.1 | |
| STARTMRK [21] | TDF/FTC/RAL | 1.3 | 0.9 | 1.9 | |
| TOKEN [31] | ABC/3TC/EFV | 1.1 | 0.5 | 2.4 | |
| DAYANA [4] | TDF/FTC/NVP | 1.0 | 0.4 | 2.4 | |
| ALTAIR [23] | TDF/FTC/ATV/r | 1.3 | 0.7 | 2.6 | |
| A5202 [30] | ABC/3TC/EFV | 0.7 | 0.6 | 0.9 | |
| | TDF/FTC/ATV/r | 1.0 | 0.8 | 1.2 | |
| | ABC/3TC/ATV/r | 0.8 | 0.6 | 1.0 | |
| PEPFAR [2,3] | AZT/3TC/NVP | 1.2 | 1.1 | 1.3 | |
| | TDF/FTC/NVP | 1.0 | 0.9 | 1.1 | |
| | TDF/3TC/NVP | 0.9 | 0.8 | 1.1 | |
| A5175 [24] | AZT/3TC/EFV | 0.9 | 0.6 | 1.2 | |
| Frankfurt [5] | TDF/FTC/NVP | 0.7 | 0.4 | 1.1 | |
| GS 934 [20] | AZT/3TC/EFV | 0.6 | 0.4 | 0.8 | |
| ECHO [26] | TDF/FTC/RPV | 1.0 | 0.7 | 1.4 | |
| ASSERT [22] | ABC/3TC/EFV | 0.7 | 0.5 | 0.9 | |

**Virological Failure**

| Risk Ratio | Lower Limit | Upper Limit | Risk Ratio and 95% CI |
|---|---|---|---|
| 4.3 | 0.5 | 36.1 | |
| 1.0 | 0.3 | 3.7 | |
| 1.6 | 0.4 | 7.7 | |
| 1.4 | 0.9 | 2.3 | |
| ----- | ----- | ----- | |
| 0.9 | 0.2 | 4.2 | |
| 0.9 | 0.2 | 3.6 | |
| 0.8 | 0.6 | 1.1 | |
| 1.0 | 0.7 | 1.4 | |
| 0.7 | 0.5 | 0.9 | |
| 1.1 | 0.8 | 1.5 | |
| 0.6 | 0.5 | 0.9 | |
| 0.5 | 0.3 | 0.8 | |
| ----- | ----- | ----- | |
| 0.6 | 0.2 | 1.5 | |
| 0.5 | 0.3 | 1.0 | |
| 0.4 | 0.2 | 0.7 | |
| 0.3 | 0.1 | 1.6 | |

0.1 0.2 0.5 1 2 5 10  Favors TDF/FTC/EFV  Favors Comparator

**Figure 2.** Relative risk (RR) and 95% confidence interval (CI) for treatment and virological failure in comparative studies: RR and 95% CI for studies comparing TDF/3TC/NVP, TDF/FTC/NVP, TDF/3TC/EFV, and TDF/FTC/EFV to another regimen are depicted. Regimens containing non-US Food and Drug

Among patients with virological failure on a TDF-containing regimen, the NRTI-resistance mutation K65R emerged frequently with TDF/3TC/NVP, less frequently with TDF/FTC/NVP or TDF/3TC/EFV, and rarely with TDF/FTC/EFV. In the following sections, we summarize published studies on the ARV activity and pharmacokinetics of NVP compared with EFV, and 3TC compared with FTC, to determine whether differences among these ARV pairs might explain the relative efficacies of the TDF-containing regimens.

### ARV Activity and Pharmacokinetics of EFV and NVP

EFV is more potent in vitro than NVP against both wild-type and drug-resistant HIV-1 variants. In cell culture, EFV $EC_{50}$s are >50-fold lower than those of NVP (reviewed in [36]). In biochemical assays, EFV $IC_{50}$s are >25-fold lower than those of NVP [36]. Most NNRTI-resistance mutations also reduce NVP susceptibility more than EFV susceptibility (Supplementary Table 2).

In the 2 largest RCTs that compared EFV- and NVP-containing initial ARV regimens, virological failure was higher in subjects receiving NVP [37, 38]. The 2NN trial randomized 1216 patients to 4 arms containing d4T/3TC plus NVP once daily vs NVP twice daily vs EFV once daily vs EFV + NVP once daily. There was no difference in the proportion of virological failures in the NVP once and twice daily arms. Virological failure in the pooled NVP arms (265 of 607, 43.7%) was significantly higher than in the EFV arm (151 of 400, 37.8%; $P$ = .02). In the NNRTI substudy of the FIRST trial, 228 subjects were randomized to NVP or EFV with 2 NRTIs (n = 110) or 2 NRTIs plus a PI (n = 118) [38]: virological failure was significantly higher in the NVP (54 of 117, 46%) vs EFV arms (33 of 111, 23%; $P$ < .02). EFV has been associated with significantly decreased virological failure relative to NVP in multiple large retrospective studies, including a large South African study of 2817 subjects, and 2 studies in the United States and United Kingdom containing a total of 1414 subjects [39–41].

Despite wide interindividual pharmacokinetics, both EFV and NVP have steady-state plasma half-lives usually exceeding 20 hours (Viramune Package Insert, http://www.boehringer-ingelheim.com/products/prescription_medicines/hiv_aids.html; Sustiva Package Insert http://www.bms.com/products/Pages/prescribing.aspx, last accessed 1 May 2011). NVP administered 400 mg once daily or 200 mg twice daily were similarly efficacious in the 2NN and ARTEN studies, although the 400 mg daily dose may be associated with an increase in toxicity [37, 42] and lower NVP trough levels

[43]. These attributes of daily NVP may have been contributed to the higher treatment failure in the DAUFIN and Boehringer-Ingelheim studies [6, 7], particularly if drug dosages were frequently missed.

### ARV Activity and Pharmacokinetics of 3TC and FTC

3TC and FTC are oxathiolane-cytosine analogs that selectively inhibit HIV replication. Like other NRTIs, 3TC and FTC must be triphosphorylated intracellularly before they can competitively inhibit endogenous deoxycytidine triphosphate (dCTP) and cause chain termination. The chemical structures of 3TC and FTC differ only by the presence in FTC of fluorine at the 5'-position of its cytosine ring. Several studies suggest that FTC may have greater ARV activity than 3TC, with the $EC_{50}$ of FTC 3-fold–10-fold lower than 3TC in cell culture (reviewed in [44]). However, the most clinically relevant difference may be the difference in intracellular half-lives between 3TC-TP and FTC-TP. The intracellular half-life of 3TC-TP appears to be shorter and more variable than that of intracellular FTC-TP: 6–30 hours [45] compared with approximately 36–39 hours [46]. Decreased intracellular half-life of 3TC-TP vs FTC-TP would potentially make 3TC-containing regimens more susceptible to individual missed drug doses, particularly when paired with other ARVs with relatively short half-lives.

### ARV Regimens Are More Than the Sum of Their Parts

The possible inferiority of TDF/3TC/NVP compared with AZT/3TC/NVP despite the greater ARV activity and lower toxicity of TDF compared with AZT underscores the concept that ARV regimens are more than the sum of their parts. This was illustrated several years ago in an analogous scenario in which the majority of subjects in several studies receiving TDF/3TC/ABC for initial ARV therapy developed virological failure and drug resistance within 12 weeks [47, 48]. In contrast, AZT/3TC/ABC—a regimen that was once an alternative regimen for initial ARV therapy—was rarely associated with early virological failure (Supplementary Figure 1). The cross-resistance engendered by K65R to TDF, 3TC, and ABC is likely to have been a contributing factor because this mutation emerged in approximately one-half of the TDF/3TC/ABC virological failures.

Whether the higher virological failure rate of TDF/3TC/NVP also results from a low-genetic barrier to resistance is not known for certain. K65R emerged frequently with TDF/3TC/NVP, less frequently with TDF/FTC/NVP or TDF/3TC/EFV, and rarely with TDF/FTC/EFV. Therefore, the risk of

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*Figure 2 continued.* Administration-approved antiretrovirals (ARVs) or ARV combinations are not shown. RR for prospective studies are depicted as black points, and RR for retrospective studies are depicted as gray points. Points to the left of midline represent improved virological efficacy for the tenofovir (TDF)-containing regimen. Points to the right of midline represent improved virological efficacy for the comparator regimen. Abbreviations: AZT, zidovudine; 3TC, lamivudine; ABC, abacavir; ATV/r, boosted atazanavir; ddI, didanosine; EFV, efavirenz; FTC, emtricitabine; LPV/r, boosted lopinavir; NVP, nevirapine; NVP XR, extended-release nevirapine; RAL, raltegravir; RPV, rilpivirine; TDF, tenofovir.

K65R emergence may be diminished by the substitution of EFV for NVP, and possibly by FTC for 3TC. However, both treatment and virological failure are multifactorial, and it would be an oversimplification to attribute the differences among these 4 regimens solely to their vulnerability to an individual mutation.

## CONCLUSIONS

Many countries are in the process of revising their national guidelines to reflect the WHO 2010 Treatment Guidelines. TDF/3TC/NVP will be increasingly used, because it is likely to be the least costly of the 4 WHO-recommended, TDF-containing regimens. However, if TDF/3TC/NVP is associated with a higher failure rate, this will rapidly lead to escalating costs because of the increased need for second-line therapy. Because patients in resource-limited regions undergo less frequent laboratory monitoring and are at higher risk of developing drug resistance than patients in well-resourced regions [49], further study of TDF/3TC/NVP is urgently required before this regimen is widely deployed for initial ARV therapy.

## Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online (http://cid.oxfordjournals.org). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

## Notes

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