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Research Article

Efficacy of Once Daily Lamivudine Versus Emtricitabine Both in Combination with Tenofovir Disoproxil Fumarate and Efavirenz in Antiretroviral-Naive, HIV-1 Infected Zambian Individuals

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Introduction

Over the past decade, a number of antiretroviral therapy regimens have emerged as highly potent and safe combinations to treat HIV. Currently recommended Antiretroviral Therapy (ART) effectively suppress HIV replication below detectable limits, prevent the potential emergence of resistant viruses, boost CD4 cell counts and thereby delay disease progression. Sub-Saharan Africa accounts for approximately 68% of the global burden of HIV infections [1]. With improving access to ART, more conveniently dosed and patient-friendly regimens are needed to minimize the demanding daily therapeutic schedules for patients and maximize adherence. In resource-limited settings, cost is another important consideration for effective management of the increasing number of patients in need of ART.

The Zambian 2007 HIV Treatment Guidelines for adults recommended the use of Tenofovir Disoproxil Fumarate (TDF), Emtricitabine (FTC) and Efavirenz (EFV) as the preferred first-line ART regimen for eligible HIV infected adults. In 2008, the Zambian Ministry of Health (MOH) procured generic tenofovir disoproxil fumarate/lamivudine (TDF/3TC) in fixed-dose combination to be used with either EFV Once-Daily (OD) or Nevirapine (NVP) twice daily (BD). This decision was based on significant cost savings for the government compared to procurement of TDF/FTC fixed-dose combinations. The cost differences per patient per year between the FTC and 3TC based generic formulations were estimated to be USD 30. The estimated yearly savings of updating the treatment guidelines with 3TC instead of FTC translated to USD 13,800,000 if the generic TDF/3TC/EFV was procured in place of the generic TDF/FTC/EFV [2]. However, no clinical trials had previously evaluated and compared once-daily 3TC/TDF against FTC/TDF in terms of efficacy and safety in ARV-naive HIV-1 infected individuals.

Lamivudine (3TC) is a synthetic dideoxynucleoside analogue, that inhibits reverse transcriptase leading to potent *in vitro* and *in vivo* antiviral activity against both HIV-1 and hepatitis B virus (HBV) [3,4]. Emtricitabine (FTC), is a cytosine nucleoside which inhibits HIV-1 reverse transcriptase leading to viral DNA termination during replication. Estimates of *in vitro* anti-HIV potencies of 3TC and FTC that use 50% inhibitory concentration to assess antiretroviral efficacy have yielded conflicting results depending on the host cell type and the strain of HIV-1 used in the assay. One such study found no significant difference in antiretroviral activity between 3TC and FTC in monocyte-derived macrophages, which are the primary cell types for HIV-1 infection *in vivo* [5]. A more recent study argued that a dose-response curve slope may be a more accurate measure of drug potency than is comparison of 50% inhibitory concentration alone; the authors found that in hybrid B- and T-lymphocytes, FTC led to a significantly faster rate of decline in drug-sensitive HIV-1 virus at 50% and 95% inhibitory concentrations than did 3TC at the same inhibitory concentrations [6]. A short-term study of FTC and 3TC monotherapy in patients naïve to both drugs found a statistically significant (but not clinically significant) difference in the cumulative antiretroviral efficacy of the two drugs among 19 patients taking FTC 200mg once daily and 21 patients taking 3TC 150 mg twice daily over 10 days (-1.14 log10 *vs.* -1.01 log10 copies/mL, p =0.04) [7]. A larger proportion of patients receiving FTC than receiving 3TC also achieved plasma viral load levels <400 copies/mL, although the study was not powered for this end point, and the finding was not statistically significant. The only serious adverse event recorded was considered unrelated to the study drug.

Previous trials (FTC-302 and FTC-303) showed equivalence of 3TC and FTC in combination with Zidovudine (ZDV) or stavudine (d4T) and a Non-Nucleoside Reverse Transcriptase Inhibitor (NNRTI) or a Protease Inhibitor (PI) [8,9]. In both these trials, 3TC was dosed as 150mg twice daily. The EPV 2001 and Gilead 903 extension studies, as well as two small studies from Senegal and Italy, evaluated the OD dosing of 3TC 300mg [10-13]. Recently, a study done in China among HIV and Hepatitis B virus (HBV) co-infected individuals showed 90% of them had HIV RNA levels <400 copies/mL whereas 71% had HBV DNA <1,000 copies/mL by 48 weeks of being on TDF, 3TC and EFV regimen [14]. None of these studies compared 3TC 300mg directly to FTC.

Recently, cohort studies have revealed lower efficacy in 3TC-based TDF formulations compared to FTC-based regimens. Evaluating the data from the AIDS Therapy Evaluation in the Netherlands (ATHENA) nationwide HIV cohort, Rockx et al. found the use of 3TC as part of cART was associated with poorer virological outcomes compared to FTC-based cART [15]. These findings would be particularly concerning, as the 2010, 2013 and subsequently the 2016 WHO guidelines for treatment and prevention of HIV, recommend either 3TC or FTC in a

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fixed-dose combination with TDF, plus EFV as the preferred first line option for initiation of cART in HIV infected adults and adolescents [16-18]. Lamivudine-containing combinations are generally cheaper than those containing FTC, an important consideration with expansion of eligible patients for ART initiation to now all HIV infected populations [2,19]. However, the fears of poorer clinical outcomes with 3TC-based formulations are based on observational data, and Ford et al. (2015) note in an editorial commentary that these findings contradict the null difference finding from 3 randomized clinical trials, concluding that there is insufficient evidence to suggest the two drugs are not interchangeable [20,22]. Both sets of authors suggest that additional clinical trials, especially those among ART-naïve patients, would provide important evidence that could have bearings on future guidelines.

We designed a clinical trial comparing the efficacy and safety of once-daily fixed-dose combination of 3TC/TDF/EFV with once-daily fixed-dose combination FTC/TDF/EFV in HIV-1 infected ARV naïve individuals in Zambia.

Methods

Participants

This trial was an open-label, randomized non-inferiority trial comparing virologic suppression (viral load < 40 copies/mL) at weeks 24 and 48 between ART-naïve HIV-1 infected adults (≥18 years) receiving once-daily 3TC 300mg or FTC 200mg, combined with TDF 300mg and EFV 600mg. Participants were recruited from two primary health care clinics and the national referral hospital outpatient HIV facility in Lusaka, Zambia. Participants were included if they were aged 18 years or older, naïve to ART (without prior history of ART for their own health or for the prevention of mother-to-child transmission). All had to meet the eligibility criteria for initiation of ART according to the 2010 national HIV treatment guidelines, and to provide informed consent.

Pregnant and lactating women, individuals with severely impaired liver (Alanineaminotransferase (ALT) or Aspartate Amino Transferase (AST) ≥ 200 IU/L) or kidney (creatinine clearance < 50mL/min) function were excluded from the study. Participants who had laboratory values outside the predefined ranges (absolute neutrophil count <500 cells/μL, haemoglobin<8.0g/dL, platelet count <50,000 cells/μL) as well as those with recent or present use of illicit drugs, psychiatric illness or Hepatitis B infection were also excluded. The University of Zambia Biomedical Research Ethics Committee reviewed and approved the study protocol and the informed consent. The approval number is FWA00000338.

Procedures

In this open-label, non-inferiority study, patients were randomly assigned in a one-to-one ratio to receive either FTC/TDF/EFV or 3TC/TDF/EFV in a once-daily fixed-dose combination. Co-formulated emtricitabine/tenofovir disoproxil fumarate/efavirenz and co-formulated generic lamivudine/tenofovir disoproxil fumarate/efavirenz were packaged in bottles containing 30 tablets (30 day supply). Randomisation was done by generating a set of sequentially numbered opaque envelopes, which were opened by the study nurse at the time of randomisation. Neither clinical staff nor patients were masked to treatment arm assignments.

Patients were clinically and biologically assessed at screening, at week 0 (baseline), and weeks 2, 4, 8, 12, 16, 20 24, 36 and 48 according to the national guidelines for HIV treatment. Determination of blood pressure, pulse, weight and body temperature was done at all study visits while height was only measured at baseline. At the screening visit, a urine pregnancy test (β- HCG) was performed for all female participants of childbearing potential. All participants were screened for hepatitis B using hepatitis B surface antigen (HBsAg), and for syphilis using rapid plasma reagin. Patients who tested positive were managed according to the national guidelines. Spot urine protein was measured by dipstick at the screening visit and at weeks 12, 24, and 48. In addition, HIV viral load was done at baseline and weeks 24 and 48 using the quantitative PCR with the Roche Amplicor version 1.5. Detectable viral loads between 40 and 1000 copies/mL at weeks 24 and 48 were confirmed with a second measurement within a month to rule out viral load blips. Further plasma HIV viral load samples were obtained at early discontinuation and when the investigators suspected treatment failure based on clinical or immunological signs and symptoms. A plasma sample for genotype evaluations was performed on all samples with confirmed viral load >1,000 copies/mL after 24 or 48 weeks of therapy.

Participants were asked about adverse events at each visit and a symptom-directed physical examination was performed. Adherence to therapy was assessed using the standard national adherence checklist and reinforced at every visit.

The primary endpoint was the proportion of patients at week 48 with HIV RNA of less than 40 copies per mL, and also the proportion of patients with Grade 3 or 4 adverse event requiring discontinuation of therapy. Secondary efficacy points were the proportion of patients with HIV RNA less than 40 copies per mL at week 24 and the antiretroviral resistance profiles of patients experiencing virological failure. Safety endpoints included the incidence of adverse events, serious adverse events, discontinuations due to adverse events, and medical intervention/therapy due to adverse events.

Statistical Analysis and Study Design

In order to demonstrate the non-inferiority of once-daily 3TC/TDF/EFV compared to FTC/TDF/EFV, we needed to show that the lower limit of the confidence interval for the observed difference in virological failure between the two regimens did not cross the pre-specified 'delta'.

Based on previous studies, we estimated the virologic response rates to be 80% [22-24]. A non-inferiority margin of 12% was chosen to allow for additional statistical uncertainty involved in the derivation of the statistical margin. This value was within the range of guidance provided to industry for design and analysis of non-inferiority studies of ART for HIV treatment and is lower than that used in similarly designed protease inhibitor non-inferiority studies [22-31].

Assuming a drop-out rate of 7.5% in each treatment arm, a two-sided alternative and a type I error of 0.05, a sample size of 328 (164 in each treatment arm) was to provide 80% power to detect a maximum allowable difference of 12% in the response rates to establish non-inferiority of TDF/3TC/EFV versus TDF/FTC/EFV in achieving viral suppression (HIV-1 RNA <40 copies/mL after 48 weeks).

Non-parametric inferential statistical methods were used for data analysis. The tests used were the Mann Whitney test, Chi-squared test, two-sample t test, and the Cuzick test for trend across ordered categories as specified in the tables.

Results

334 patients were randomised with 166 assigned to the FTC/TDF/EFV arm and 168 to the 3TC/TDF/EFV arm. The patients enrolled in the two arms of the study had a comparable baseline profile (Table 1).

A total of 26 patients, 11 (6.6%) and 15 (8.9%) from the FTC/TDF/EFV and 3TC/TDF/EFV arms respectively, discontinued the study drugs at different time points due to various reasons: adverse events (hepatotoxicity; 3 patients), lost to follow-up (17), transferred out (5), and deaths (2). Four (4) participants from the FTC/TDF/EFV arm and five (5) from the 3TC/TDF/EFV arm discontinued study drugs before 24 weeks. The 7 and 10 participants from, respectively, the FTC/TDF/EFV and 3TC/TDF/EFV arms discontinued after 24 weeks.

The proportion of patients achieving virologic suppression at 24 weeks was 90.1% in the FTC/TDF/EFV arm and 86.5% in the 3TC/TDF/

Factors	TDF/FTC/EFV N=166 (49.7%)	TDF/3TC/EFV N=168 (50.3%)	p-value
Age, (years)	35 (30, 43)	35 (29, 41.5)	0.406*
Female, n (%)	97 (58.4%)	98(58.3%)	0.985#
Height, (cm)	163.5 (159, 171)	164 (158, 171)	0.700t
Weight (kg)	59.0 (52.0, 67.0)	56.0 (50.0, 64.0)	0.085*
BMI (kg/m^2)	21.5 (18.9, 24.9)	20.4 (18.5, 23.5)	0.056
CD4+ cell count (cells/μL)	142.5 (69.0, 261.0)	168.5 (85.5, 269.5)	0.115*
Viral load (copies/mL)	110,000 (44,000-320,000)	130,000 (31,000-300,000)	0.576*
CrCl (mL/min)	79.5 (69.0, 94.0)	81.0 (70.0, 95.0)	0.529*
Renal Dysfunction			
Normal	120 (72.3%)	125 (74.4%)	
Mild	43 (25.9%)	36 (21.4%)	
Moderate	3 (1.8%)	6 (3.6%)	
Severe	0 (0%)	1 (3.6%)	0.772[tr]
ALT (U/L)	22.0 (15.0, 38.0)	21.0 (16.0, 31.0)	0.380*
Hepatitis B, n (%)	5 (3.05%)	19 (12.6%)	0.003#
Syphilis, n (%)	7 (4.22%)	14 (8.48%)	0.111#
Proteinuria			
Nil	160 (96.4%)	154 (91.7%)	
1+	5 (3.01%)	8 (4.76%)	
2+	1 (0.6%)	6 (3.57%)	0.113
WHO clinical stage			
1	59 (35.5%)	51 (30.4%)	
2	36 (21.7%)	37 (22.0%)	
3	63 (38.0%)	66 (39.3%)	
4	8 (4.82%)	14 (8.33%)	0.514#

Table 1: Baseline Characteristics.

*=Mann Whitney test, #=Chi-squared test, values are Median (IQR) unless stated, [t]=two sample t test, BMI=Body mass index, ALT= Alanine Aminotransferase, [tr]=Cuzick test for trend across ordered categories, CrCl= Creatinine Clearance (calculated using the CKD-EPI formula), Hepatitis B= Hepatitis B surface antigen, Syphilis= rapid plasma reagin positivity.

EFV arm giving a proportional difference of -3.6%. At 48 weeks there was a similar trend in virologic suppression; 90.1% for FTC/TDF/EFV versus 85.3% for 3TC/TDF/EFV with a proportional difference of -4.8% (Table 2, Figure 1 and Figure 2).

The changes in viral loads in the two arms were similar with majority of patients suppressed at week 24 and maintaining suppression at week 48 (Table 3). The changes in viral loads from baseline, weeks 24 and 48 were comparable with slightly more patients achieving virologic suppression in the FTC/TDF/EFV arm though statistically insignificant

Virologic Suppression	FTC/TDF/EFV Proportion (97.5% CI)	3TC/TDF/EFV Proportion (97.5% CI)	Proportional difference (97.5% CI)
HIV-1 RNA< 40 copies/mL (week 24)	90.1% (84.8%, 95.4%)	86.5% (80.5%, 93.5%)	-3.6% (-27.0%, 19.7%)
HIV-1 RNA< 40 copies/mL (week 48)	90.1% (84.8%, 95.4%)	85.3% (79.0%, 91.5%)	-4.8% (-28.1%, 18.4%)

Table 2: Virologic suppression at 24 and 48 weeks.

CD4 Change	FTC/TDF/EFV N=166 (49.7%)	3TC/TDF/EFV N=168 (50.3%)	p-value
CD4 at baseline, (cells/μL))	142.5 (69.0,261.0)	168.5(85.5,69.5)	0.115*
CD4 at 24 weeks, (cells/μL)	269.0 (178.0,389.0)	286.0 (170.0,178.0)	0.900*
CD4 at 48 weeks, (cells/μL)	310.0 (220.0,467.0)	348.5 (223.0,491.0)	0.289*

Table 3: Mean CD4 change at 24 and 48 weeks.

*=Mann Whitney test

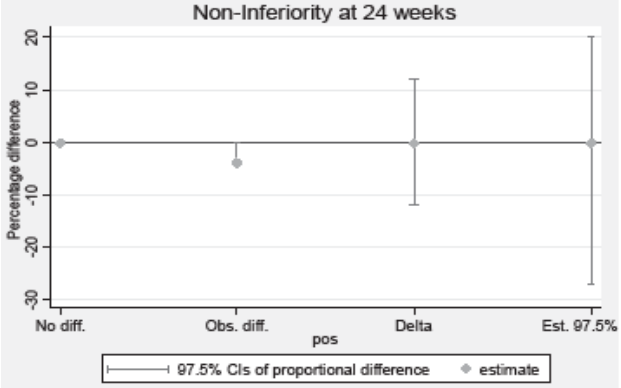

Figure 1: Non-inferiority at 24 weeks.

(Figure 3). The trends observed show similar responses in changes in viral loads at various time points.

The immunological response represented by CD4 values at each time point independently tested by treatment group were also comparable with median CD4 T- cell values of 269 and 286 (week 24) and 310 and 348 (week 48) for FTC/TDF/EFV and 3TC/TDF/EFV arms respectively. Comparison of the changes in CD4 T- cell count values by treatment group using a paired t-test however showed a statistically significantly larger rise in CD4 T- cell values in the FTC/TDF/EFV arm at both weeks 24 and 48 weeks (Figure 4). The margin of difference was wider at week 24 and this margin narrowed greatly by week 48 of treatment.

The clinical response in both arms was similar with more than 96% of patients asymptomatic for HIV disease at week 24 and more than 98% at week 48 with no patient having WHO stage 4 disease. Two patients from the 3TC/TDF/EFV arm died of cervical cancer and pulmonary tuberculosis.

There were a total of 23 patients who failed treatment by having a confirmed viral load of >40 copies/mL. Of these, 13 (56.5%) were on the FTC/TDF/EFV arm whereas 10 (43.5%) were on the 3TC/TDF/EFV arm (p= 0.647 by Mann Whitney test). Treatment failure occurred by week 24 weeks in 9 out of 10 patients in the TDF/3TC arm and 11 out of 13 in the TDF/FTC arm. 8 of the 23 patients with virologic failure had missed at least one pharmacy visit.

The patients failing treatment had genotypic analysis done and all had HIV-1 subtype C of which 9 had wild type virus. Among the 14 with resistant virus, the Nucleoside Reverse Transcriptase Inhibitor (NRTI) resistance mutations K65R and M184V were found in all 14 patients (100%) and T69D in 2 patients (14.3%). The non-nucleoside reverse transcriptase inhibitor (NNRTI) associated mutation K103N was found

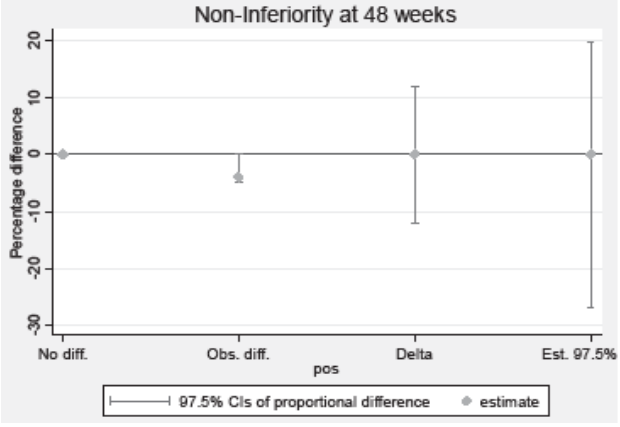

Figure 2: Non-inferiority at 48 weeks.

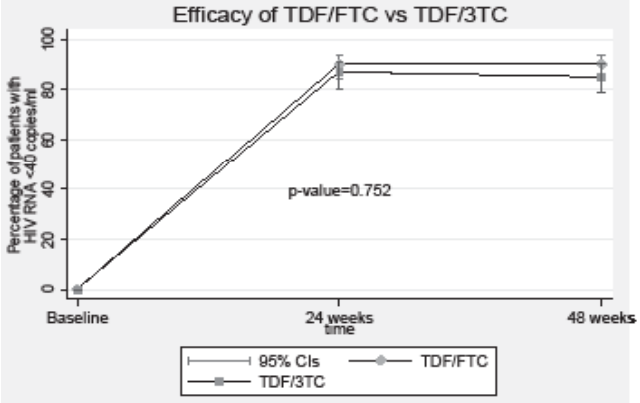

Figure 3: Viral load change at 24 and 48 weeks.

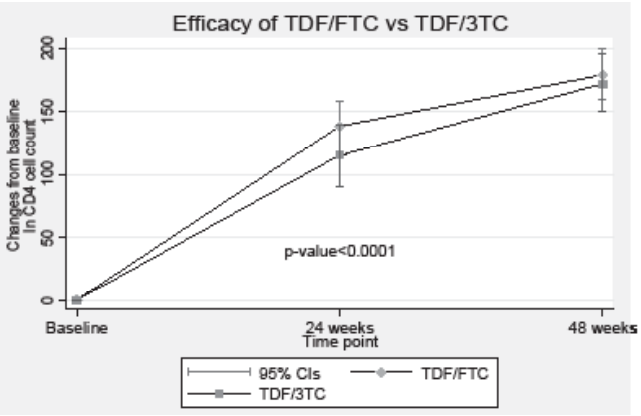

Figure 4: Mean CD4 change at 24 and 48 weeks.

in 10 patients, whereas Y181C was seen in 6 patients. Two patients had V106M and V179D mutations. No patient had any protease inhibitor associated mutations.

All patients failing therapy were switched to AZT/TDF/FTC/LPV-r second-line therapy except for those who had wild type virus, who were instead counselled to emphasize adherence.

Discussion

We sought to establish whether fixed dose once daily 3TC/TDF/EFV is as efficacious and safe as FTC/TDF/EFV fixed dose combination in the ARV naïve HIV-1 infected population. Our findings suggested no evidence of inferiority of once daily 3TC 300mg compared to once daily FTC 200mg both combined with TDF 300mg and EFV 600mg. It was also established that treatment failure rates were similar between the FTC and 3TC containing arms with similar genotype resistance pattern observed among both groups. Our data are in agreement with other trials which proved efficacy of once-daily 3TC in combination with AZT and an NNRTI (EPV 2001) or with TDF and an NNRTI in virologically suppressed HIV infected patients already on ART (Gilead 903). Furthermore, our findings are similar to the earlier trials which showed equivalent antiviral efficacy and safety of FTC 200 mg once daily compared to 3TC 150 mg twice daily and also agree with the systematic review and meta-analysis of randomized trials performed by Ford, et al. [8,9,20-22]. The findings of TDF-associated mutations (K65R) in all the patients with resistant mutations also suggest a higher risk of development of this mutation in HIV subtype C among patients on TDF containing regimens as seen in other cohorts [32]. This study is relevant especially to our region since once daily 3TC and once daily FTC, co-formulated with similar combinations (TDF/EFV), are largely used as first line agents in resource limited settings and recommended

by WHO as the preferred first line agents. It also compared patients with similar baseline characteristics and practices who were taking the two different formulations over the same period of time and therefore unlikely to have important differences, which could influence outcomes.

Our findings however are not consistent with those from a cohort study from Europe which showed lamivudine to show worse virologic outcomes compared to emtricitabine [15]. This cohort study was from a different geographical location with different baseline patient characteristics and median years for ARV initiation.

Individuals on FTC/TDF/EFV arm had a more robust change in CD4 T cell values compared to those on 3TC/TDF/EFV and this difference was statistically significant. By week 48, patients on the 3TC/TDF/EFV arm however seemed to have a comparable but slightly lower overall rise in CD4 values from baseline. This difference, though statistically significant, may not have been clinically significant as the clinical improvement in the two arms was similar regardless of the difference in immunological functional improvement. The fact the immunological profile was almost similar at week 48 may suggest that 3TC/TDF/EFV has a sluggish initial rise in CD4 T-Cell values and a more robust rise after 24 weeks of treatment.

Several primarily cost-based limitations prevented expanding the scope of some analyses. For example, lack of baseline resistance testing may have led to inabilities to detect primary resistance leading to earlier failure to ART. This type of testing could not be done due to funding limitations. The inability to estimate the drug levels of 3TC and FTC also limited the interpretation of the bioavailability of the drug impacting on resistance. In addition we could not assess adherence in detail due to non-standard adherence assessments. However there was no clinical implication seen on these as both treatment regimens had similar clinical, immunological and virologic outcomes. This study does not address the efficacy of 3TC versus FTC both in combination with TDF and NVP. This aspect could not be included in the study design due to complexity of design leading to increased cost of the study and possible confounding by regimen. Additionally, since there is no fixed dose combinations of the TDF/FTC/NVP or TDF/3TC/NVP regimens, more countries recommend the once daily fixed dose combinations of TDF/FTC/EFV or TDF/3TC/EFV.

This study provides important additional data to inform the use of a once-daily 3TC/TDF/EFV in antiretroviral-naive HIV-infected patients, a significant knowledge gap. It addresses the important question of whether this cheaper combination therapy can achieve similar antiviral activity to its counterpart FTC/TDF/EFV the two generic formulations, which are largely used as first line agents in the developing regions. This study would influence policy in such regions, on which regimen to be used due to cost implications without fears of differences in outcomes.

Conclusion

In assessing the efficacy of 3TC/TDF/EFV once daily regimens, we did not find this triple ARV combination inferior to FTC/TDF/EFV both at 24 and 48 weeks of treatment. The virologic, immunologic and clinical responses were comparable between the two regimens. This was reflected in the comparable changes from baseline in plasma HIV RNA levels and absolute CD4+ T-cell counts at weeks 24 and 48 plus the similar rates of regimen change due to treatment failure and genotypic resistance pattern. In terms of safety, both regimens were well-tolerated.

We can therefore conclude that 3TC/TDF/EFV is as efficacious and safe as FTC/TDF/EFV in treatment of HIV-1 infected ARV naïve patients. These two regimens can thus be used interchangeably without any concern over one being inferior or more toxic than the other.

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