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Original article

Efavirenz, tenofovir and emtricitabine combined with first-line tuberculosis treatment in tuberculosis–HIV-coinfected Tanzanian patients: a pharmacokinetic and safety study

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Background: To evaluate the effect of rifampicin-based tuberculosis (TB) treatment on the pharmacokinetics of efavirenz/tenofovir/emtricitabine in a fixed-dose combination tablet, and *vice versa*, in Tanzanian TB–HIV-coinfected patients.

Methods: This was a Phase II open-label multiple dose pharmacokinetic and safety study. This study was conducted in TB–HIV-coinfected Tanzanian patients who started TB treatment (rifampicin/isoniazid/pyrazinamide/ethambutol) at week 1 to week 8 and continued with rifampicin and isoniazid for another 16 weeks. Antiretroviral treatment (ART) of efavirenz/tenofovir/emtricitabine in a fixed-dose combination tablet was started at week 4 after initiation of TB treatment. A 24-h pharmacokinetic sampling curve was recorded at week 8 (with TB treatment) and week 28 (ART alone). For TB drugs, blood samples at 2 and 5 h post-dose were taken at week 3 (TB treatment alone) and week 8 (with ART).

Results: A total of 25 patients (56% male) completed the study; 21 had evaluable pharmacokinetic profiles. The area under the concentration–time curve 0–24 h post-dose of efavirenz, tenofovir and emtricitabine were slightly higher when these drugs were coadministered with TB drugs; geometric mean ratios (90% CI) were 1.08 (0.90, 1.30), 1.13 (0.93, 1.38) and 1.05 (0.85, 1.29), respectively. For TB drugs, equivalence was suggested for peak plasma concentrations when administered with and without efavirenz/tenofovir/emtricitabine. Adverse events were mostly mild and no serious adverse events or drug discontinuations were reported.

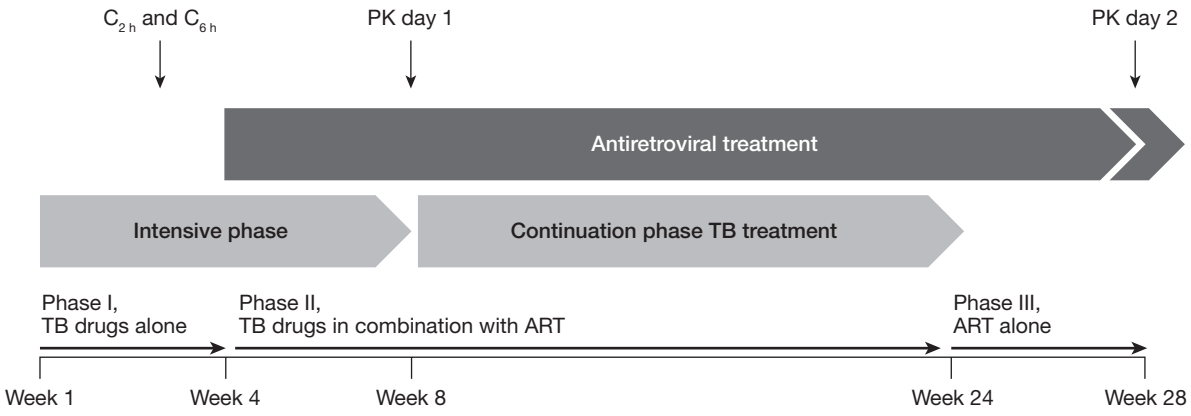
Conclusions: Coadministration of efavirenz, tenofovir and emtricitabine with a standard first-line TB treatment regimen did not significantly alter the pharmacokinetic parameters of these drugs and was tolerated well by Tanzanian TB patients who are coinfected with HIV.

Introduction

Coinfection with tuberculosis (TB) and HIV is an important public health problem. Nearly 40 million people are living with HIV worldwide and one-third is coinfected with TB [1–3]. The majority of TB cases in people living with HIV/AIDS occur in Africa, where 39% of people who develop TB are HIV-positive. The continent accounts for 82% of new TB cases living with HIV worldwide [1]. Management of the dual infection requires combining TB treatment and antiretroviral treatment (ART) which markedly decreases the risk of morbidity and mortality to those patients [4].

Coadministering TB drugs with ART precipitates pharmacokinetic (PK) interactions, mostly caused by rifampicin. Rifampicin is a well-known inducer of many iso-enzymes of the hepatic cytochrome P450 (CYP) enzyme system, which metabolizes a large number of drugs [5]. In addition, it stimulates the expression of the multi-drug resistance transporter, P-glycoprotein

Figure 1. Trial study design



ART, antiretroviral treatment; $C_{2\,h}$, plasma concentration at 2 h; $C_{6\,h}$, plasma concentration at 6 h; PK, pharmacokinetic; TB, tuberculosis.

[6,7]. Current guidelines for ART in patients also using rifampicin recommend the use of efavirenz plus two nucleoside reverse transcriptase inhibitors [8,9]. Although combined use of rifampicin and efavirenz leads to an average decrease of approximately 18–26% in efavirenz exposure due to induction of the CYP2*B6* enzyme [10,11], several studies have demonstrated adequate virological response in patients using both drugs [4,12].

A fixed-dose combination (FDC) tablet of efavirenz, tenofovir and emtricitabine was approved by the US Food and Drug Administration in 2006. This combination tablet is widely used as it is highly effective and can be administered as a single tablet once-daily [13]. There are no data available on the combined use of a rifampicin-based TB regimen and this FDC in TB–HIV-coinfected patients. The aim of this study was to evaluate the effect of rifampicin-based TB treatment on the PK and safety of the FDC of efavirenz, tenofovir and emtricitabine. The secondary objective was to evaluate the effect of this FDC on the PK of the TB medication.

Methods

Study design and population

This was a multiple-dose open-label three-period Phase II PK and safety study. The enrolment started in November 2008 and ended in February 2010. Patients included were 18–65 years old and TB–HIV-coinfected with $CD4^+$ T-cell counts of 50–350 cells/mm^3 (later amended to 0–350 cells/mm^3). Patients were excluded if they were already using ART, they were pregnant or breastfeeding, they had liver dysfunction (objectified by biochemistry results, and hepatitis B and C antigen tests) and if they were hypersensitive to either of the regimens. Another exclusion criterion was a Karnofsky score <40 based on the activities a patient could perform. The study protocol was approved by the Institutional Review Board of the Kilimanjaro Christian Medical University Centre, Moshi, Tanzania, and the National Institute for Medical Research, Dar-es-salaam, Tanzania. Written informed consent was obtained from each patient. Eligible patients were admitted at Kibong'oto National Tuberculosis Hospital, Kilimanjaro, Tanzania for the first 8 weeks of TB treatment (intensive phase).

Patients <50 kg were given TB treatment consisting of rifampicin 450 mg, isoniazid 225 mg, pyrazinamide 1,200 mg and ethambutol 825 mg, all administered once daily for 8 weeks. If patients were >50 kg, they received rifampicin 600 mg, isoniazid 300 mg, pyrazinamide 1,600 mg and ethambutol 1,100 mg once daily for 8 weeks. After a negative sputum culture at week 8, TB treatment was continued with rifampicin and isoniazid for another 16 weeks. TB drugs were administered 30 min after a light breakfast. TB drugs were provided by the Tanzanian National TB program, and they were manufactured by Sandoz, Mumbai, India and donated by Novartis. The ART regimen of a once-daily single FDC tablet of efavirenz 600 mg, tenofovir 300 mg and emtricitabine 200 mg (Atripla®; Merck & Co., Inc., Foster City, CA, USA) was initiated at week 4 after starting TB treatment and was administered together with the TB drugs.

The study was divided in three phases (Figure 1). From week 1 to the end of week 4, patients were exposed to TB drugs alone (phase I). From week 5 to the end of week 24 they were exposed to concomitant use of TB drugs and an FDC tablet containing efavirenz, tenofovir and emtricitabine (phase II). After 24 weeks, when

TB treatment was ended, patients were exposed to ART alone (phase III). Both TB and HIV treatment were administered under supervised care including directly observed treatment for 8 weeks. After 8 weeks, patients were discharged. A one-month dose of efavirenz, tenofovir and emtricitabine and standard TB treatment was dispensed and patients were asked to come for follow-up visits at the clinic every month.

Blood sampling and bio-analysis procedures

Eight weeks after starting TB treatment, a 24-h PK sampling session was carried out. Samples were taken 5–20 min before directly observed intake of efavirenz, tenofovir and emtricitabine (t=0) and 1, 2, 3, 4, 6, 8, 10, 12, 16 and 24 h later. At 28 weeks, 4 weeks after cessation of TB treatment, intensive plasma PK sampling was repeated. In addition, for the determination of rifampicin, isoniazid, pyrazinamide and ethambutol plasma concentrations, blood samples were taken after initiation of TB treatment at 3 weeks (without ART) and 8 weeks (with ART). These blood samples were drawn at 2 and 6 h after observed medication intake to be able to assess ('catch') peak plasma concentrations of TB drugs, which was taken as highest of the two. Breakfast (non-milky tea and/or porridge) was provided 5–20 min after pre-dose sampling, together with TB and/or HIV medication. An aliquot of 6 ml of blood was collected per time point and centrifuged at 2,800 rpm for 10 min. Within 1 h, plasma was stored at -20°C for 1 day and then shifted to a -80°C freezer until transportation on dry-ice to Radboud University, Nijmegen, the Netherlands, for bio-analysis. Plasma concentrations of all drugs except isoniazid were assayed by validated HPLC methods [14–17].

Isoniazid was measured with liquid/liquid extraction followed by UPLC with ultraviolet detection. Accuracy was between 98% and 107%, dependent on the concentration level. The intra- and interassay coefficients of variation were <13% over the ranges of 0.051 to 15.1 mg/l. The lower limit of quantitation was 0.051 mg/l. Isoniazid containing samples were stable (<5% loss) for ≥12 months at -80°C.

Safety and tolerability monitoring

Baseline clinical, haematology and biochemistry parameters were taken and, when applicable, a pregnancy test was done. Safety and tolerability of the trial treatment were assessed by a medical doctor on the basis of the occurrence of adverse events (AEs) about which patients were interviewed every 2 weeks during the first 8 weeks, and every 1 month after hospital discharge. The onset, severity and potential relationship of any AE to the study medication were recorded. Severity was rated according to the Common Terminology Criteria for AEs (version 4) and the Division of AIDS table for grading the severity of Adult and Paediatrics AEs. In addition, the use of concomitant medication was reported, as were the results of a physical examination including measurement of vital signs. Clinical laboratory testing (haematology and biochemistry parameters) was performed at baseline and weeks 2, 4, 6, 8, 12, 16, 24 and 28. Follow-up sputum collection, $CD4^+$ T-lymphocyte count and plasma HIV-1 RNA quantification (using Abbott Real Time HIV-1 assay) was done at baseline and weeks 4, 8, 16 and 28.

Pharmacokinetics and statistical analyses

PK parameters (area under the concentration–time curve 0–24 h post-dose [$AUC_{0-24\ h}$], minimum plasma concentration [C_{min}] and maximum plasma concentration [C_{max}]) of efavirenz, tenofovir and emtricitabine were calculated by non-compartmental analysis using WinNonlin (version 5.2; Pharsight, CA, USA). $AUC_{0-24\ h}$ was calculated using the linear-log trapezoidal rule. PK parameters, geometric means with standard deviation, geometric mean ratios (GMRs) for $AUC_{0-24\ h}$, C_{max} and C_{min} for the antiretroviral drugs with and without TB treatment and the corresponding 90% confidence intervals (CIs) were calculated. PK parameters of the antiretroviral drugs with versus without TB drugs were considered bioequivalent if the GMR and corresponding 90% CI fell completely within the 0.80–1.25 range. Equivalence was 'suggested' in case the GMR is within the 0.80–1.25 range, but with one CI limit outside this range. Inequivalence was to be concluded if the GMR and corresponding 90% CI fell completely outside the 0.80–1.25 range. Inequivalence was 'suggested' if the GMR was outside the 0.80–1.25 range, with one confidence interval inside this range [18]. PK analysis included only those patients with two evaluable PK curves (at week 8 and week 28). All statistical analyses were done in SPSS version 18.0 (SPSS Inc, Chicago, IL, USA). To ensure an evaluable PK dataset of ≥20 patients, a total of 30 patients were included (based on an expected maximum dropout of 33% during the trial after ART initiation).

Results

Study population

We screened 66 HIV-infected patients with confirmed smear-positive pulmonary TB. Overall, 38 (58%) patients were not eligible: 19 had a $CD4^+$ T-cell count >350 cells/mm^3, 8 had a $CD4^+$ T-cell count <50 cells/mm^3 (before protocol amendment), 5 were already on ART, 2 had a positive hepatitis antigen test, 3 had a Karnofsky score <40 and 1 had relapse TB. Of the 28 (42%) patients enrolled in the trial, three withdrew consent; the remaining 25 patients completed follow-up and were evaluable for analysis. For PK evaluation four patients were

excluded due to non-adherence or incorrect dosing, as indicated by undetectable plasma concentrations for efavirenz, tenofovir and emtricitabine prior to observed intake during the intensive PK sampling day. Hence, 21 subjects were qualified for the PK evaluation. Among the patients who completed follow-up, 14 (56%) were male, the median (IQR) baseline age and bodyweight were 32 years (27.5–42.5) and 48.4 kg (43.5–52.8), respectively. in our study population, mean ±SD bodyweight increased significantly from 53.4 ±8.0 kg at week 8 to 56.8 ±6.5 kg at week 28. The median (IQR) CD4+ T-cell count at baseline was 155 cells/mm^3 (71–208) and the median (IQR) viral load (VL) was 129,779 (71,214–310,141) copies/ml. Baseline characteristics are displayed in Table 1.

Table 1. Enrolment characteristics of the study participants

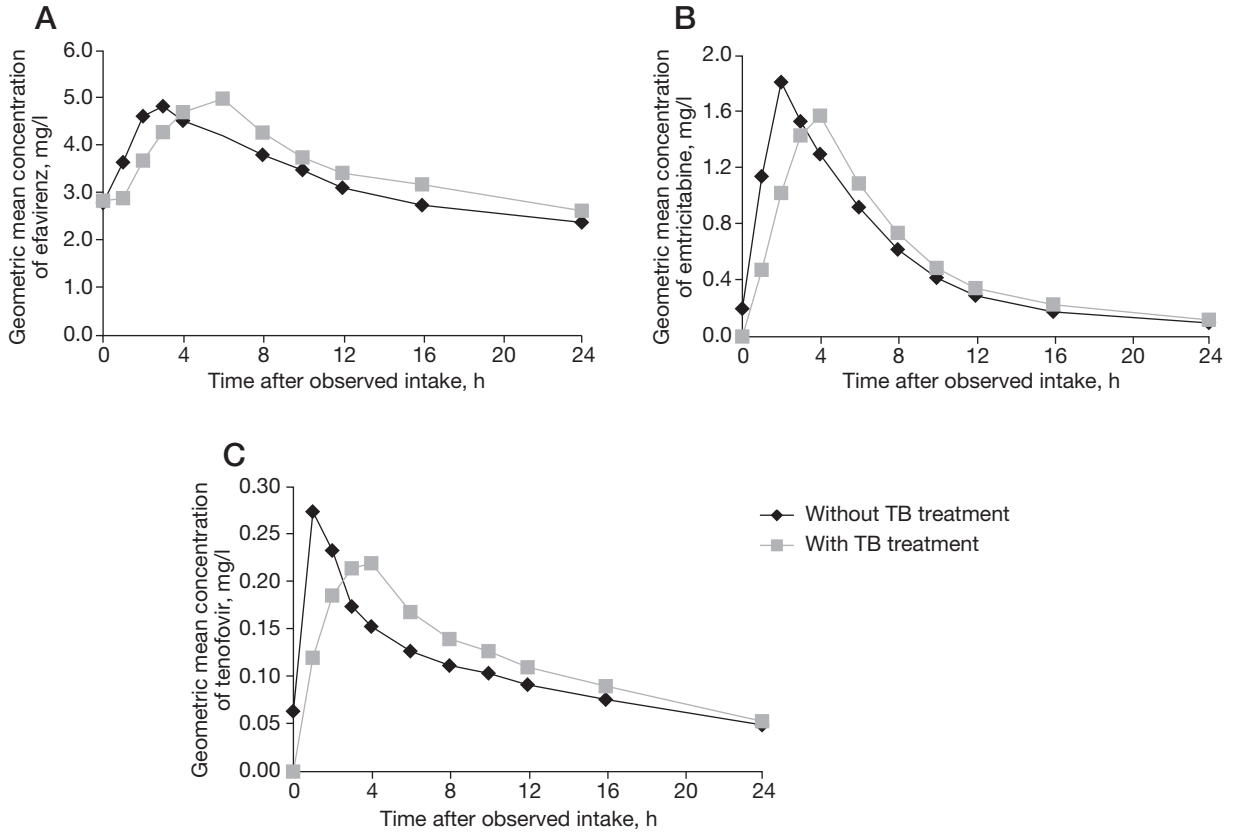
Characteristics	Total
Patients followed-up, *n*	25
Male	14 (56)
Age, years	32 (27.5–42.5)
Weight, kg	48.4 (43.5–52.8)
CD4+ T-cell count, cells/mm^3	155 (71–208)
HIV viral load, copies/ml	129,779 (71,214–310,141)

Values are *n* (%) for categorical variables and median (IQR) for continuous variables unless otherwise indicated.

Pharmacokinetics of antiretroviral treatment

Figure 2 illustrates the effect of the TB treatment on the geometric mean concentration–time profiles of the ART. The average efavirenz $AUC_{0-24\ h}$, C_{max} and C_{min} were slightly higher when efavirenz was coadministered with rifampicin-based TB treatment. The GMRs lie within the range of 0.80–1.25 with the upper limit of the 90% CIs for $AUC_{0-24\ h}$ and 24 h plasma concentration ($C_{24\ h}$) just above 1.25 (Table 2). GMRs (90% CI) were 1.08 (0.90, 1.30), 1.02 (0.8, 1.23) and 1.11 (0.90, 1.37) for $AUC_{0-24\ h}$, C_{max} and $C_{24\ h}$, respectively, which means that equivalence was suggested (that is,

Figure 2. Plasma concentration–time curves



Curves of mean plasma concentration versus time are shown for **(A)** efavirenz, **(B)** emtricitabine and **(C)** tenofovir after observed intake of a fixed-dose combination tablet (efavirenz/tenofovir/emtricitabine) alone and in combination with tuberculosis (TB) treatment.

no effect of rifampicin on the efavirenz PK). Overall, 3 of the 21 (14%) patients had subtherapeutic efavirenz plasma concentrations (<1.0 mg/l [19]) after observed intake at one or both PK sessions: one patient at week 8 only, one patient at week 28 only and one at both PK days. Potentially toxic plasma levels (>4.0 mg/l [19]) after observed intake were found in 10 (48%) of the patients. Eight of these patients had potentially toxic levels at both PK sessions. Two patients had a C_{min} and C_{max} both >10 mg/ml. The time to reach the maximum concentration (T_{max}) was observed to be higher during coadministration with TB drugs.

Similarly, for tenofovir and emtricitabine the GMRs and 90% CIs of the PK parameters suggest a slightly higher exposure in combination with TB drugs. GMRs (90% CIs) of $AUC_{0-24\ h}$, C_{max} and $C_{24\ h}$ for tenofovir were 1.1 (0.93, 1.4), 0.98 (0.78, 1.4) and 1.09 (0.86, 1.4), respectively, while for emtricitabine they were 1.05 (0.85, 1.3), 0.97 (0.75, 1.3) and 1.3 (1.04, 1.5), respectively. The PK parameters ($AUC_{0-24\ h}$, C_{max}, $C_{24\ h}$, T_{max}, elimination half-life, volume of distribution and clearance) for efavirenz, tenofovir and emtricitabine are summarized in Table 2.

Pharmacokinetics of tuberculosis drugs

The plasma concentrations of all TB drugs tended to be slightly lower during coadministration in combination with ART. The bio-equivalence approach applied to the C_{max} values for TB drugs suggested bioequivalence of

Table 2. Pharmacokinetic parameters of efavirenz, tenofovir and emtricitabine alone and in combination with tuberculosis treatment

PK parameter	Week 28 (ART alone)[a]	Week 8 (ART with TB treatment)[a]	GMR (90% CI)
Efavirenz			
$AUC_{0-24\ h}$, h•mg/l	81 (58, 114)	88 (60, 129)	1.08 (0.90, 1.30)
C_{max}, mg/l	5.7 (4.2, 7.5)	5.7 (4.3, 7.7)	1.02 (0.80, 1.23)
C_{min}, mg/l	2.4 (1.6, 3.5)	2.6 (1.6, 4.2)	1.11 (0.90, 1.37)
T_{max}, h[b]	3.1 (1.0–10.1)	4.0 (1.1–8.0)	–
$t_{1/2}$, h	27 (25, 35)	29 (20, 47)	1.08 (0.77, 1.41)
Cl/F, l/h	7.4 (5.3, 10.4)	6.8 (4.6, 10.1)	0.92 (0.77, 1.11)
V/F, l	313 (232, 421)	301 (236, 383)	0.96 (0.72, 1.29)
Tenofovir			
$AUC_{0-24\ h}$, h•mg/l	2.6 (2.1, 3.2)	2.9 (2.4, 3.5)	1.13 (0.93, 1.38)
C_{max}, mg/l	0.33 (0.26, 0.41)	0.32 (0.26, 0.40)	0.98 (0.78, 1.38)
C_{min}, mg/l	0.05 (0.04, 0.06)	0.05 (0.04, 0.07)	1.09 (0.86, 1.38)
T_{max}, h[b]	1.0 (0.9–8.0)	2.1 (0.0–6.2)	–
$t_{1/2}$, h	14 (12, 15)	11 (10, 12)	0.81 (0.75, 0.86)
Cl/F, l/h	94 (76, 117)	83 (69, 100)	0.88 (0.73, 1.08)
V/F, l	1,852 (1,438, 2,385)	1319 (1,099, 1,584)	0.71 (0.59, 0.86)
Emtricitabine			
$AUC_{0-24\ h}$, h•mg/l	14 (12, 16)	15 (11, 18)	1.05 (0.85, 1.29)
C_{max}, mg/l	2.1 (1.8, 2.3)	2.0 (1.5, 2.7)	0.97 (0.75, 1.25)
C_{min}, mg/l	0.10 (0.09, 0.12)	0.12 (0.10, 0.16)	1.26 (1.04, 1.53)
T_{max}, h[b]	2.0 (1.0–8.0)	3.0 (0.0–6.0)	–
$t_{1/2}$, h	6.6 (5.8, 7.5)	7.3 (6.1, 8.6)	1.10 (0.93, 1.31)
Cl/F, l/h	18 (15, 21)	17 (13, 22)	0.96 (0.77, 1.18)
V/F, l	171 (139, 210)	180 (124, 261)	1.05 (0.75, 1.48)

[a]Data are geometric mean (90% CI). [b]Time to reach the maximum concentration (T_{max}) is presented as median (IQR). ART, antiretroviral therapy; $AUC_{0-24\ h}$, area under the concentration–time curve 0–24 h post dose; Cl/F, clearance; C_{max}, maximum plasma concentration; C_{min}, minimum plasma concentration; GMR, geometric mean ratio; PK, pharmacokinetic; $t_{1/2}$, elimination half-life; V/F, volume of distribution.

Table 3. Maximum plasma concentrations of rifampicin, isoniazid, pyrazinamide and ethambutol alone and in combination with antiretroviral treatment based on sampling at 2 h and 6 h post-dose

Drug	GM Week 2 (without HIV drug)	GM Week 8 (with HIV drug)	GMR (90% CI)
Rifampicin, mg/l	4.60	3.97	1.16 (0.88, 1.53)
Isoniazid, mg/l	1.24	1.18	1.06 (0.85, 1.31)
Pyrazinamide, mg/l	31.64	35.95	0.88 (0.78, 0.99)
Ethambutol, mg/l	2.09	2.11	0.99 (0.78, 1.26)

GM, geometric mean; GMR, geometric mean ratio.

the TB drugs when given alone versus in combination with ART (Table 3).

Efficacy

In total, 25 patients completed follow-up to the end of week 28. At week 4 of the study (prior to ART) they had a median (IQR) VL of 134, 204 copies/ml (71,414–401,004). At week 28 (after starting ART), 17 (68%) patients had an undetectable VL (<40 copies/ml). The remaining 8 (32%) patients had a median (IQR) VL of 51 copies/ml (40–532). Among 23 (92%) of the patients, $CD4^+$ T-cell counts were available both at baseline and at the end of the study. Their median (IQR) $CD4^+$ T-cell count increased from 119 cells/mm^3 (69–203) to 238 cells/mm^3 (147–424; $P<0.01$; Wilcoxon's signed-rank test).

By the end of 8 weeks of TB treatment, 19 of 25 (76%) patients had negative sputum smears (confirmed by negative sputum cultures) and continued with rifampicin and isoniazid for 16 weeks. A total of 6 (24%) patients had positive sputum smear results after 8 weeks of treatment, of which 2 had negative and 4 had a positive cultures for *Mycobacterium tuberculosis*. Drug susceptibility testing of the isolates obtained from these four patients showed normal susceptibility patterns and therefore, those four patients continued with intensive phase TB treatment for another 4 weeks. At week 12, sputum smear results of all four patients were negative. Of the four, two had an undetectable VL at week 16, the remaining two had VLs of 659 copies/ml and 8,032 copies/ml each. All 25 patients had negative sputum culture results at the end of TB treatment.

Safety

A total of 12 (48%) patients developed elevated biochemistry parameters. These included elevated alkaline phosphatase in 11 patients (all grade 1 except for two patients who had grade 2), elevated creatinine in three patients (two of which were grade 2 and one of which was grade 3) and elevated pancreatic amylase and alanine aminotransferase in one patient each (both grade 1). The patient with grade 3 elevation of creatinine recovered spontaneously. A total of 19 (76%) patients developed decreased haematological parameters. These were mostly leucopenia and neutropenia (12 subjects each), and were all grade 1. Four patients had anaemia, of which two were grade 1, one was grade 2 and the remaining one was grade 3. Two patients had thrombocytopenia (one grade 1 and the other grade 2). The laboratory abnormalities had all resolved at completion of the study.

Tolerability

Before administration of ART (phase 1), 24 of 25 (96%) patients had experienced one or more clinical AEs; with a total of 99 events (65% grade 1, 34% grade 2 and 1% grade 3). After starting ART (phase 2), 23 of the 25 (92%) subjects experienced ≥1 new or aggravated AEs at some time during follow-up. These were, in total, 95 AEs and mostly mild disturbances (64% grade 1, 33% grade 2 and 3% grade 3). There were no serious AEs reported and no modifications or discontinuations of treatment were done. Overall, 13% of the clinical events were judged to have no relationship to the drugs, 83% had either a doubtful or possible relationship, and 4% had a possible relationship. At the end of follow-up, all events were recovered except for four patients who still had either loss of appetite, body rash, general body weakness or constipation.

A total of 50% of the 10 patients who had toxic levels of efavirenz experienced a clinical AE compared to 40% among patients without toxic levels ($P=0.70$) and 30% of the events were grade 2 for the group with toxic levels versus 38.5% for the subtherapeutic group ($P=0.23$). Lab events were reported in 90% of the patients with toxic levels of efavirenz and 93% of patients without toxic levels. Two patients with efavirenz concentration >10 mg/l throughout showed only mild (grade 1) AEs.

Discussion

This study is the first to report on the interactions of efavirenz, tenofovir and emtricitabine with first-line rifampicin-based TB treatment. No interactions were observed in the PK analysis. The observed slightly higher $AUC_{0-24\ h}$, C_{max} and $C_{24\ h}$ of efavirenz when coadministered with the rifampicin-based TB treatment in our study is consistent with a recent study that showed the absence of an effect of rifampicin on efavirenz PK when patients are poor metabolizers of CYP2*B6* [20]. Our data are also in agreement with recent studies in South Africa, Tanzania and India showing that efavirenz concentrations do not decrease when it is coadministered with a rifampicin-based TB treatment regimen [21–23]. The metabolism of efavirenz is extensively influenced by pharmacogenetic factors [21,24–26]. A single nucleotide polymorphism at position 516 on the CYP2*B6* gene has been widely reported to play an important role in the metabolism of efavirenz and nevirapine [27–29]. Genetic polymorphisms with CYP2*B6* occur in all populations, and this may affect the exposure to efavirenz and its susceptibility to rifampicin-based enzyme induction [30–32]. The slightly higher efavirenz levels during combined TB and HIV treatment in our study could be explained by genetic differences [20,23,25].

A once-daily dose of efavirenz 600 mg during TB therapy is reported to be adequate [22,33,34]. However, in our study, potentially toxic plasma levels (>4.0 mg/l) were observed in 48% of the patients. Also subtherapeutic

levels of efavirenz (<1.0 mg/l) were found in 14% of the patients. The observed high intervariability of drug levels suggests inter-patient differences in the expression of the drug metabolizing enzymes [11]. For observed potentially toxic levels, no further action was taken as the patients were already discharged in a good condition. The levels occurred both before and during coadministration with TB treatment. Nevertheless the frequent presence of high levels in our African patient population may warrant the use of therapeutic drug monitoring of efavirenz plasma concentrations to improve the safe use of ART during TB treatment, and the need for individual dose adjustment [10].

Comparison of exposure to tenofovir with and without rifampicin-based TB treatment did not suggest any effect of rifampicin, although PK equivalence (lack of interaction) could not be concluded. Studies elsewhere have also shown no difference in tenofovir concentration while observing bioequivalence [15]. However, participants in these studies were healthy volunteer subjects who received tenofovir for 7–14 days, which implies that less potential factors may have affected the PK of tenofovir in those subjects. PK parameters may be different in patients as compared to healthy volunteers due to changes brought by both HIV and TB infection [35]. It is known that tenofovir is eliminated unchanged by glomerular filtration and active tubular secretion [36], while rifampicin is extensively metabolized in intestinal and hepatic metabolism [7], which minimizes the interactions. Emtricitabine has also been reported to have no PK drug–drug interactions with other antiretroviral drugs and rifampicin.

The T_{max} of emtricitabine, tenofovir and efavirenz were longer when coadministered with rifampicin than without rifampicin, although the median difference was only 1 h for all three drugs. With regard to efavirenz, this may be due to delayed absorption upon coadministration of rifampicin. Clearance of efavirenz could be affected in patients with genotype CYP*2B6*. We did not analyse genetic aspects of these patients, hence further studies are warranted. No large differences were found in clearance and volume of distribution.

This study showed a small decrease in levels of TB drugs with versus without coadministration of efavirenz, tenofovir and emtricitabine. We do not consider this to be clinically significant. Studies elsewhere have also found no statistically significant effect of efavirenz on rifampicin [5,7,22,37]. In our study, rifampicin and isoniazid peak plasma concentrations were lower than the reference peak values (8–24 mg/l rifampicin and 3–5 mg/l isoniazid) [38]. One possible explanation could be that the values in this study, obtained from either 2 or 6 h after intake, were not the actual peak values. Secondly, our patients took medications just after food intake which is known to lower concentrations of rifampicin and isoniazid [39].

All patients had a positive response to treatment in terms of sputum culture and decrease of VL. An important finding of our study is that we detected non-adherence in four patients included in the trial when pre-dose samples were analysed. This can be explained by the fact that the patients were discharged home after 8 weeks, and subjects were asked to come for follow-up visits at the clinic every month. We recommend strong coordination between the national TB, community DOT system and the AIDS control programmes.

The main shortcoming of this study is that we did not look into genetic factors of the patients, which could have provided an explanation of high efavirenz drug levels and for the extent of the interaction between efavirenz and rifampicin-based TB treatment. In addition, the study did not examine the effect of anti-TB treatment on intracellular PK of tenofovir and emtricitabine, as intracellular diphosphate or triphosphate levels are associated with clinical effects. It is possible that rifampin-containing TB treatment may not influence plasma PK but could affect intracellular PK through induction or inhibition of drug transporters.

In conclusion, our findings suggest that coadministration of the standard first-line TB treatment regimen with efavirenz, tenofovir and emtricitabine does not alter PK parameters. The combination is tolerated well by Tanzanian TB–HIV-coinfected patients. Hence, a combination of efavirenz, tenofovir and emtricitabine may be considered in managing HIV infection in African patients who are coinfected with TB.

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Disclosure statement

The authors declare no competing interests.

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