Poster # 837

Effect of Antituberculosis Therapy on the Pharmacokinetics of Efavirenz in Children

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INTRODUCTION

- Tuberculosis (TB) is one of the most common opportunistic infections (OIs) affecting children with HIV.
- Globally, efavirenz (EFV)-based antiretroviral therapy (ART) is the preferred regimen in HIV–infected children aged 3 to 14 years or adults with TB coinfection who need rifampin-containing therapy.
- As in adults, World Health Organization (WHO) recommend no EFV dose adjustment with concurrent anti-TB therapy. Thus, the same EFV weight-band dosing recommendation is used irrespective of need for concurrent TB treatment.
- EFV is metabolized primarily by CYP2B6, with minor contribution from CYP2A6 and UGT2B7. Rifampin is a known inducers of the CYP2B6, while isoniazid is an inhibitor CYP2A6. In most individuals (especially non-slow metabolizers of EFV), the net effect of first-line anti-TB regimen is induction of EFV metabolism leading to reduce plasma concentrations.
- In adults, the effect of anti-TB therapy on EFV pharmacokinetics (PK) is modest, so EFV dose adjustment is generally not recommended.
- In children, we propose that the net effect of anti-TB therapy on EFV PK differs quantitatively from that in adults. Thus, recommendations in adults may not be extrapolated to children.
- We hypothesized that the standard EFV weight-band dosages may not achieve comparable PK parameters in children with TB/HIV coinfection compared to those with HIV alone.

Study objective and endpoints

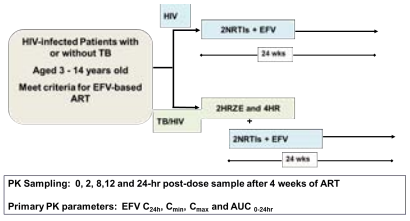
- Primary objective: To examine the effect of rifampin-containing anti-TB therapy on EFV PK in HIV/TB co-infected children aged 3 – 14 years compared those with only HIV.

- Primary endpoint: Plasma PK parameters (C_{max}, C_{min}, C_{24h}, $AUC_{0\text{-}24h}$ and CL/F) of EFV in children with TB/HIV coinfection on anti-TB therapy compared to those with only HIV.
- Secondary endpoint: Safety, tolerability, and HIV RNA suppression rate at 3 and 6 months of ART between the two groups

METHODS

- A two-arm parallel assignment PK study was performed at Komfo Anokye Teaching Hospital, Kumasi, Ghana (**Fig. 1**).
- Eligible HIV-infected children with or without TB were enrolled and initiated on two NRTIs + EFV. Children with OIs other than TB were excluded from the study.
- Participants were seen in follow-up at 2 weeks after starting ART, and then monthly for 6 months or for up to a month after completion of TB therapy.
- Clinical evaluations, CBC, LFTs, renal function were performed at scheduled visits, as well as when indicated by side effects.
- PK sampling was performed after 4 weeks on ART.
- On the day of sampling, blood samples were drawn into EDTA tubes, immediately placed on ice and centrifuged within 30 minutes and plasma stored at -80ºC until assay.
- EFV plasma concentrations were determined using gas chromatography with mass spectrometry (LC-MS) at University of Cape Town Pharmacology Laboratory.
- PK analysis: PK parameters were determined by non-compartmentalized analysis (NCA).
- Statistical analysis: Pharmacokinetic parameters were summarized using descriptive statistics. Differences in PK parameters between children with TB/HIV coinfection and those with only HIV were compared by rank sum test.

Fig 1. Study design



RESULTS

- Baseline characteristics are shown in **Table 1**.
- Children with TB/HIV coinfection children had 53% lower EFV C_{24h}, 37% lower C_{min} and 28% lower $AUC_{0\text{-}24h}$ (**Table 1**).
- C_{min} and C_{max} were lower in the TB/HIV co-infected group (**Fig. 2**)
- The proportion of children with EFV C_{min} < 1 µg/mL was 47.4% in co-infected children and 17.6%, respectively in those with HIV only (P = 0.008).
- EFV-based ART was well tolerated in both groups with no treatment discontinuations due to drug side effects.
- Virologic suppression (VS) rate at 6 months of ART was lower in TB/HIV co-infected children (**Fig. 3**). However, it should be noted that only 18 children with TB/HIV and 19 with only HIV had viral load data for these analysis.

Table 1. Baseline characteristics. Median (IQR) values reported.

Characteristic	All (N = 72)	HIV (N = 34)	TB/HIV (N = 38)	*P* value
Age (years)	7.5 (4.9 – 10.2)	9.3 (6.0 – 11.0)	6.2 (4.4 – 10.0)	**0.025**
Weight (kg)	17.5 (14.1 – 23.5)	22.0 (15.1 – 27.7)	15.3 (14.1 – 23.5)	**0.005**
Height (cm)	113.0 (96.0 – 129.0)	124.5 (102.0 – 137.0)	104.5 (94.0 – 120.0)	**0.005**
EFV dose (mg/kg)	14.7 (12.4 – 16.1)	13.0 (11.7 – 15.1)	15.0 (14.2 – 16.5)	**0.008**
Female n (%)	37 (51.4%)	17 (50.0%)	20 (52.6%)	**1.000**

Table 2. Median IQR PK parameters by TB coinfection status

Parameter	All (N = 72)	HIV (N = 34)	TB/HIV (N = 38)	TB/HIV:HIV PK ratio	*P* value
T_{max} (h)	2.1 (2.0 – 8.0)	2.0 (2.0 – 8.0)	2.1 (2.0 – 8.0)	1.05	0.317
C_{max} (µg/mL)	3.4 (2.5 – 4.5)	4.1 (2.9 – 5.1)	3.1 (2.3 – 4.0)	0.76	**0.031**
C_{12h} (µg/mL)	1.8 (1.2 – 2.8)	2.0 (1.5 – 3.4)	1.5 (0.8 – 2.7)	0.75	0.068
C_{last} (µg/mL)	1.3 (0.7 – 2.4)	1.7 (1.2 – 3.3)	0.8 (0.6 – 1.6)	0.47	**0.001**
T_{min} (h)	12.0 (0.2 – 12.2)	11.9 (0.2 – 12.1)	12.0 (0.2 – 12.3)	1.01	0.671
C_{min} (µg/mL)	1.4 (0.8 – 2.5)	1.6 (1.2 – 2.8)	1.0 (0.6 – 2.3)	0.63	**0.042**
$AUC_{0\text{-}24h}$ (µg *hr/mL)	51.0 (32.0 – 68.3)	56.4 (47.3 – 70.4)	40.4 (26.1 – 64.6)	0.72	**0.017**
CL/F (L/hr)	5.9 (3.8 – 8.5)	5.5 (3.4 – 7.6)	6.5 (4.5 – 10.9)	1.18	0.085
Vz/F (L)	159 (96 – 245)	164 (100 – 263)	143 (94 – 226)	0.87	0.664

Fig 2. EFV PK parameters in HIV and TB/HIV co-infected children. *p<.05, ***P< .001

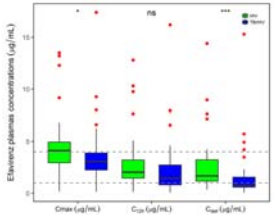
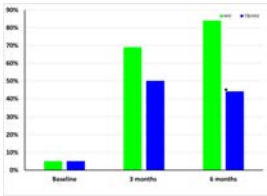


Fig. 3. Proportion of children with virologic suppressed (HIV RNA < 200 copies/mL). *Difference in VS rate is significant



CONCLUSIONS

- Rifampin-containing anti-TB therapy significantly reduces EFV concentrations in children. This is concerning as low EFV concentrations may lead to poor ART outcomes.
- As EFV-based ART is most compatible with anti-TB therapy, adequately powered studies to examined virologic outcome in TB/HIV co-infected children is urgently needed.

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