Poster # 0825

Effect of Antituberculosis Therapy on Nevirapine Pharmacokinetics in Young Children

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BACKGROUND

- Early initiation of antiretroviral therapy (ART) in persons with TB/HIV coinfection reduces mortality, but optimal ART regimens in children younger than 3 years old is severely limited.
- Nevirapine-based ART is one of 3 options recommended for HIV treatment in young children during anti-TB therapy, but pharmacokinetic (PK) or efficacy data is very scare.
- One comparative study of nevirapine PK reported 41% lower nevirapine AUC0-6h in children with TB compared to those without TB. These findings are yet to be verified or replicated.
- In this study, we compared nevirapine PK in young children with TB/HIV coinfection on concomitant anti-TB treatment to that in children without TB who are treated with similar nevirapine-based regimen and dosage.
- We also compared nevirapine PK during and after stopping anti-TB therapy in the TB/HIV co-infected children with paired samples.

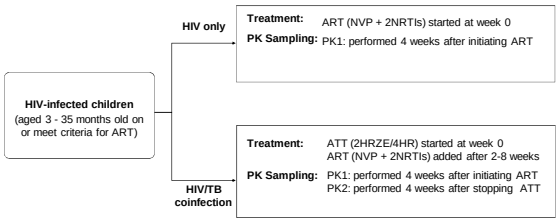


Fig. 1. Timeline of the study design. ART, antiretroviral therapy; ATT, antituberculosis therapy; E, ethambutol; NVP, nevirapine; H, isoniazid; NRTIs, nucleoside reverse transcriptase inhibitors; PK, pharmacokinetic; PK1, first pharmacokinetic sampling in HIV/TB infected children; PK2, second pharmacokinetic sampling in HIV/TB infected children; R, rifampin; TB, tuberculosis; Z, pyrazinamide.

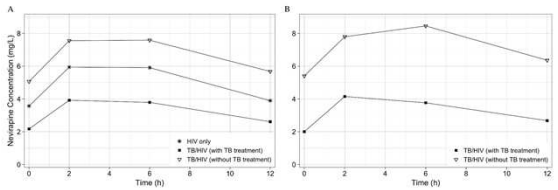


Fig. 2. Median nevirapine plasma concentration plotted by sampling time after dosing. Panel A shows the plots for all participants in each treatment group, and panel B shows plots for TB/HIV co-infected children who had paired samples on and off antituberculosis therapy

METHODS

- A two-arm parallel assignment PK study (**Fig. 1**) was performed at Komfo Anokye Teaching Hospital, Ghana.
- HIV-infected children with or without TB aged 3 to 35 months old or body weight < 10 kg were enrolled and initiated on two NRTIs + nevirapine 200 mg/m2 twice daily, with a 2-week lead in.
- Anti-TB therapy consisted of INH, RIF, PZA and EMB daily x 2 months and INH and RIF daily x 4 months using new revised dosages. In the co-infected patients, ART was started 2-8 weeks after staring TB treatment.
- PK sampling was performed after 4 weeks on ART, and in those with TB/HIV coinfection, sampling was repeated at least 4 weeks after stopping anti-TB therapy.
- Nevirapine concentrations were determined using liquid 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: Differences in PK parameters between children with TB/HIV coinfection and those with HIV were compared by rank sum test and on and off anti-TB therapy by Signed rank test. Multiple regression was applied with stepwise variable selection using AICC.

Table 1. Median (IQR) pharmacokinetic parameter estimates of nevirapine in Ghanaian children with HIV with and without tuberculosis

Parameter	All (N= 53)	HIV (N = 30)	TB/HIV (N = 23)	P value
T_{max} (hr)	2.3 (2.0 – 6.1)	2.2 (2.0 – 6.1)	5.6 (2.0 – 6.1)	0.792
C_{max} (µg/mL)	5.9 (3.7 – 8.4)	6.1 (4.4 – 8.8)	4.3 (3.1 – 6.9)	0.068
C_{min} (µg/mL)	3.5 (2.0 – 4.9)	3.7 (2.6 – 5.3)	2.6 (1.9 – 4.9)	0.187
AUC_{0-12h} (µg *hr/mL)	56.0 (35.2 – 79.6)	62.9 (40.6 – 95.3)	43.9 (30.3 – 68.9)	0.057
CL/F (L/hr)	1.4 (0.9 – 2.0)	1.3 (0.7 – 1.8)	1.6 (0.9 – 2.6)	0.150
V/F (L)	22.0 (15.7 – 33.8)	20.0 (14.0 – 33.2)	22.1 (17.6 – 39.9)	0.290
T1/2 (hr)	12.5 (8.2 – 17.8)	12.9 (8.9 – 16.0)	10.8 (7.1 - 23.2)	0.647

RESULTS

- Of the 53 children,23 (43%) had TB coinfection. The median age (range) was 1.6 (0.3 – 3.6) years old.
- In the TB/HIV co-infected children, median (range) isoniazid and rifampin dosages were 14.1 (3.3 – 24.3) and 18.8 (6.6 – 32.4) mg/kg
- Baseline characteristics of the two groups were similar except the TB/HIV co-infected children were shorter.
- Nevirapine concentrations-time profiles for the groups are shown in **Fig. 2 panel A,** and on and off anti-TB therapy in **Fig. 2 panel B**.
- PK parameters in the two groups are shown in Table 1.
- The proportion of children with nevirapine C_{min} < 3 mg/L was 61% in TB/HIV co-infected children and 31% in those with HIV only (*P* = 0.030). It was 24% off anti-TB therapy.
- In a multivariate analysis, TB coinfection and *CYP2B6* 516G>T genotype jointly influences nevirapine PK.
- Differences in PK parameters between the 2 groups was only significant in children with *CYP2B6* 516GG and not in those with GT and TT genotypes (**Fig. 3**).
- In those with paired samples, nevirapine AUC0-12h was reduced by 34% and CL/F increased by 45% during compared to after stopping anti-TB therapy (**Fig. 4**).

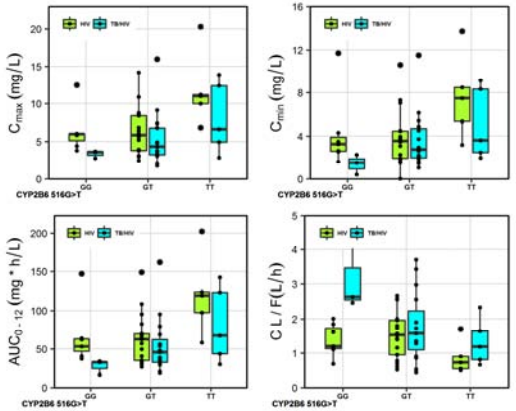


Fig. 3. Nevirapine pharmacokinetic parameters in HIV-infected children by *CYP2B6* 516G>T genotype. Difference between HIV and TB/HIV groups by genotype for C_{max}, AUC_{0-12h}, CL/F is only significant for GG genotype (*P* < 0.05) but not GT or TT genotypes. C_{min} difference between children with and without TB with GG genotype shows a trend (*P* = 0.07)

CONCLUSIONS

- Rifampin-containing anti-TB therapy reduced nevirapine exposure by 34% in our study population.
- However, a high proportion of TB/HIV co-infected children had sub-therapeutic C_{min}.
- The effect of anti-TB therapy was dependent on *CYP2B6* 516G>T genotype status, which would complicate a dose adjustment strategy.
- Nevirapine dose optimization during concomitant anti-TB therapy based on *CYP2B6* genotype is likely not feasible in countries with high TB and HIV burden given cost and need for individualized approach.
- Evaluation of more compatible alternatives to nevirapine is needed in young children.

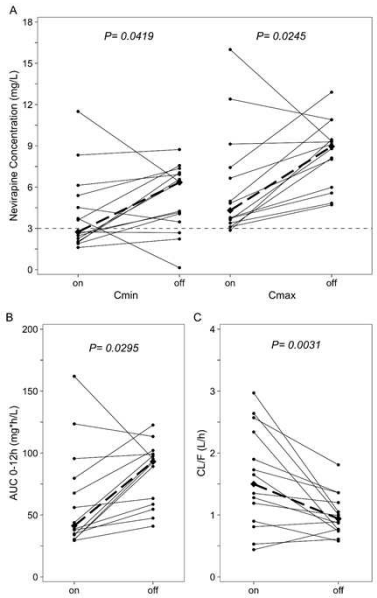


Fig. 4. Nevirapine C_{min} (panel A), C_{max} (panel A), AUC_{0-12h} (panel B)and CL/F (panel C) on and off antituberculosis therapy in 14 TB/HIV co-infected children with paired samples. Signed Rank Test P value for median change in PK parameters between the two periods (dotted line) is reported

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