

Pharmacokinetics of nevirapine in young children during combined ART and rifampicin-containing antituberculosis treatment

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Introduction

- ▶ HIV and tuberculosis (TB) common co-infections
- ▶ However, major interactions in co-treatment of TB/HIV
- ▶ Rifampicin strong inducer of hepatic enzymes



Introduction: HIV-TB cotreatment options

- ▶ Defer antiretroviral treatment
- ▶ Non-nucleoside reverse transcriptase inhibitors (NNRTIs):
 - Efavirenz (not licensed in children <3 years)
 - Nevirapine
- ▶ Nucleoside reverse transcriptase inhibitors (NRTIs):
 - Abacavir
- ▶ Protease-inhibitors (PIs)
 - Lopinavir/ritonavir

Nevirapine (NVP)

- ▶ Nevirapine: key first line antiretroviral drug in many resource-limited countries.
- ▶ Increased availability for children through Triomune Baby/Junior 3-fixed dose combination (NVP, stavudine (d4T), lamivudine (3TC))
- ▶ Pharmacokinetics (CHAPAS-1) in children: NVP exposure with Triomune Baby/Junior higher than in adults^a

Objective

To determine the plasma pharmacokinetics (AUC , C_0 , C_{max}) of nevirapine in HIV-infected children aged below 3 years of age who are concurrently treated with Triomune Baby/Junior (NVP, d4T, 3TC) and a rifampicin-containing tuberculosis-regimen.

Study Methods: study population

22 children infected with both HIV and TB recruited via University Teaching Hospital Lusaka, Department of Paediatrics, Zambia

Inclusion criteria

- HIV-infected children aged 3 months – < 3 years
- TB-infected and on rifampicin for at least 2 weeks and starting Triomune Baby/Junior

OR on Triomune Baby/Junior and starting TB-treatment

- Given informed consent

Exclusion criteria

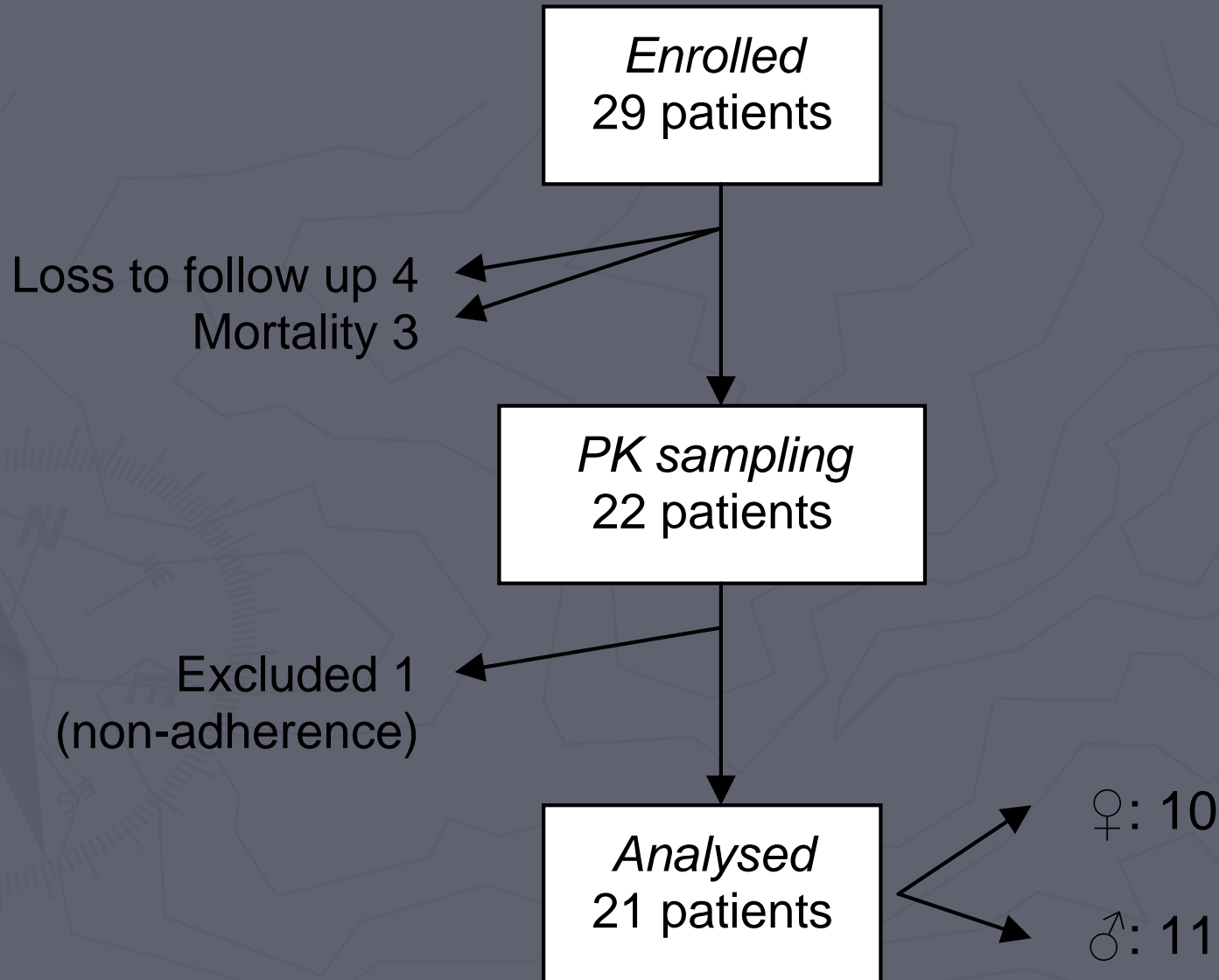
- Anemia (Hb < 8g/dL)
- Severe laboratory abnormalities
- Illnesses that influence PK (e.g. diarrhoea)
- Interacting concomitant medications

Study methods: sample collection and analysis

- ▶ Pharmacokinetic (PK) sampling after at least 4 weeks of concurrent treatment
- ▶ Limited sampling model (6-hour)^b: PK sampling *before* and 1, 2 and 6 hours *after* drug intake
- ▶ Assay of plasma concentrations: University of Cape Town, South Africa, using validated LC-MS/MS methods
- ▶ Comparison of NVP PK to 16 children without TB-treatment (CHAPAS-1)^a using multivariate linear regression

^b D. Burger. CROI 2008 (oral presentation)

Results: patient inclusion

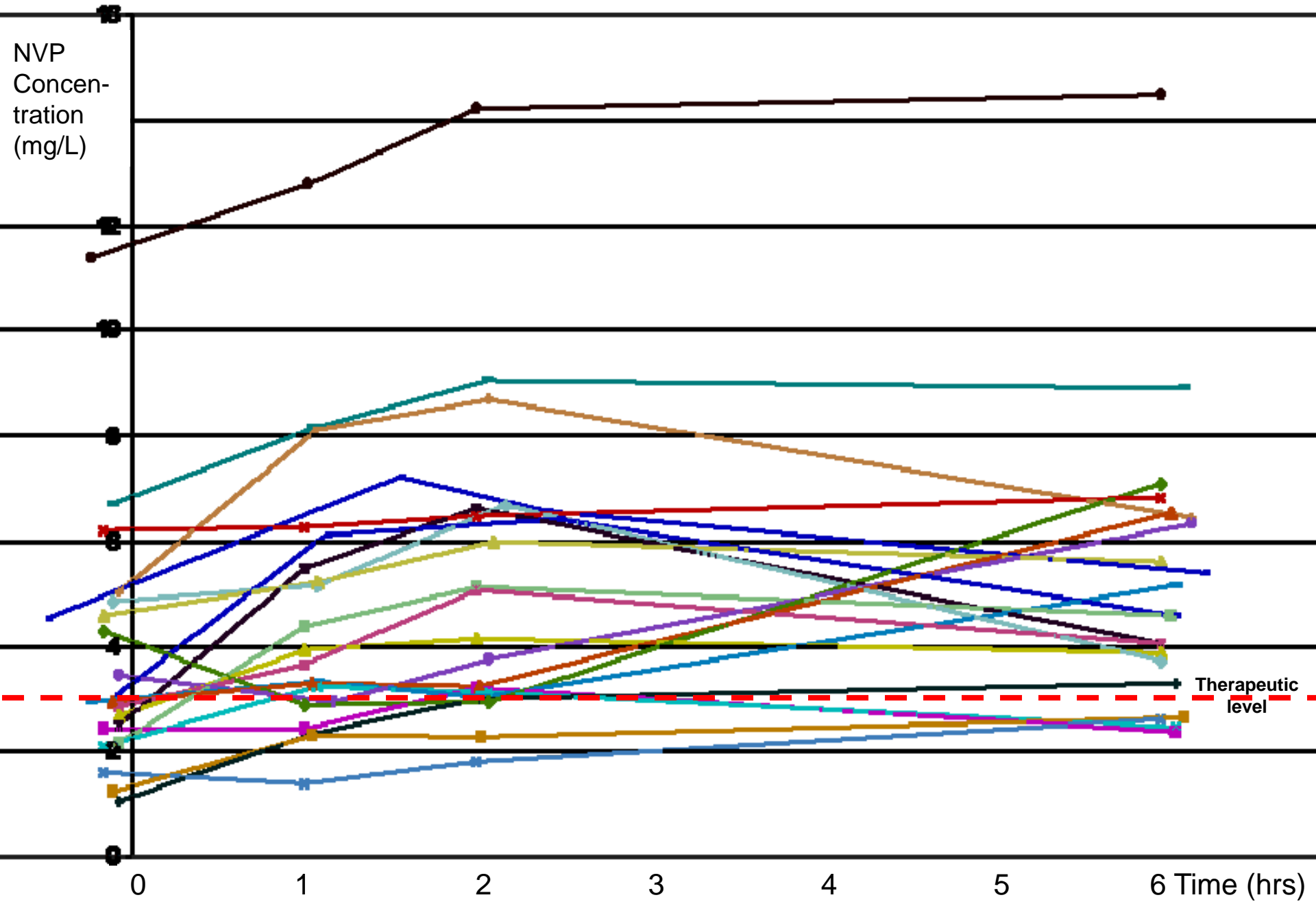


Results: demographics

	Children with TB (n=21)	Children without TB (n=16)
Age (years)	1.55 (0.66 – 3.18)	1.33 (0.56 – 2.51)
Weight (kg)	8.0 (5.1 – 10.5)	8.0 (3.6 – 12.0)
Weight-for-age Z-score	-3.6 (-5.5 – -2.01)	-2.41 (-9.3 – -0.10)
%CD4 cells	12.9 (3.9 – 33.4)	16.8 (6.0 – 25.9)
Number of girls (%)	10 (48)	8 (50)

Values are median (range) unless otherwise stated.

Individual NVP concentration vs time curves



Results: Pharmacokinetic outcomes

	Children with TB (n=21)	Children without TB (n=16)
C_0 (mg/L)	2.93 (1.06 – 11.4)	5.93 (3.28 – 18.1)
Peak concentration (mg/L)	6.33 (2.61 – 14.5)	9.59 (5.28 – 21.0)
Estimated AUC (mg*h/L)	52.0 (22.6 – 160)	90.9 (40.4 – 232)
Number with subtherapeutic levels (%)	11 (52)	0 (0)

Values are medians (range) unless otherwise stated.

Multivariate linear regression:

- ▶ 41% reduction in AUC in children with vs without rifampicin
- ▶ Effect dose/m²: 3.4% increase in AUC for each 10 mg/m² increase in nevirapine dose/m²

Discussion

- ▶ 41% decrease in NVP AUC comparable to findings in adults
- ▶ Half of patients subtherapeutic trough levels
- ▶ No data on resistance and viral load
- ▶ Doses before trough level not observed (only self-reported adherence)
- ▶ Study not powered to detect differences between subgroups

Comparison with other studies

	Zambia (n=21)	Uganda ^c (n=7*)	Thailand ^d (n=8)
Age (yrs)	1.6 (0.66-3.2)	5.0 (1.2-11)	9.7 (4.4-12)
Weight (kg)	8.0 (5.1-11)	16 (9.3-38)	19 (15-29)
NVP dose (mg/m ² /day)	349 (294-417)	NA	343 (301-525)
NVP dose (mg/kg/day)	18 (15-23)	11 (8.0-16)	NA
RIF dose (mg/kg)	12 (8.4-18)	NA	9.8 (8.3-11.8)
NVP C ₀ (mg/L)	2.9 (1.1-11)	2.9 (1.7-10)	6.5 (3.0-14)
NVP AUC (mg*h/L)	52 (23-157)	NA	85 (41-172)
NVP>3.0mg/L	48%	43%	70%

Data are medians (range). NA: not available

*Subgroup. Median age/wt/dose is given for whole group of 20 patients.

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Conclusion

- ▶ 41% reduction in NVP exposure in children <3 years of age concurrently treated with rifampicin
- ▶ Only half reaching sufficient trough levels
- ▶ More safety and efficiency data needed
- ▶ Higher NVP dose may be necessary and requires evaluation.

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