



Pharmacokinetics and drug-drug interactions of lamivudine and abacavir co-administered with antituberculosis drugs in HIV-infected children treated for multidrug-resistant tuberculosis

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Background and Objectives

Lamivudine and abacavir are used as dual nucleoside reverse transcriptase (NRTI) treatment for **first-line antiretroviral treatment in HIV-infected children (>3 months)**. **As multidrug-resistant (MDR)-TB is also prevalent in settings with high burden of TB and HIV, it is important to identify potential drug-drug interactions (DDIs) between MDR-TB treatment and NRTIs in children.**

Lamivudine is primarily renally eliminated, has low protein binding (generally <36%) and induces p-glycoprotein(1). Abacavir is extensively metabolised by the liver (8, 9),

primarily via urine diphosphate glucuronyltransferase and alcohol dehydrogenase; protein binding is ~50% and it is a substrate and possible inhibitor of p-glycoprotein. These are all sites for possible DDIs with MDR-TB drugs.

We describe the pharmacokinetics of and potential DDIs between lamivudine and abacavir and routine drugs used for MDR-TB treatment in HIV-infected children.

Methods

Data - 54 HIV+ children on NRTI regimen: 27 on MDR-TB treatment (MDR-TB group) and 27 without TB (control group).

Lamivudine dosed at 4 mg/kg twice daily or 8 mg/kg once daily and abacavir at 8 mg/kg dose twice daily or 16 mg/kg once daily, as per local guidelines(2).

MDR-TB treatment according to WHO recommendations.

Blood samples: -1, 0 and 1, 3, 7, 5 or 10 hr post NRTI dose (2 patients were on once daily evening dosing, sampled at 10, 11, 13, 15 and 17 hours the following day).

Assays - Samples were processed with liquid-liquid extraction method using ethyl acetate, followed by LC-MS/MS detection. LLOQ for both drugs was 0.024 mg/L.

Model-NONMEM 7.4.3 with FOCE-I was used to develop the population PK model.

PsN, Pirana and Xpose were used in the model building process for data exploration, visualization and creation of diagnostics.

Allometric scaling was used to account for the effect of body size (using either total body weight or fat-free mass) and age was tested using a sigmoid Emax maturation model(3). Bayesian priors based on reports from larger comparable populations(4)(5); and 20% uncertainty was used to stabilize the models.

MDR-TB treatment, as single combined variable, and selected single TB drugs, frequently used in our study, were tested as a categorical covariate.

BLQ values were handled by the M6 method(6) and for all imputed values the additive error was inflated by LLOQ/2.

Results

Two-compartment models with first-order elimination and transit compartment absorption described well the PK of both lamivudine and abacavir.

Allometric scaling with body weight adjusted for the effect of body size, after which maturation could be identified: clearance was predicted to reach half its mature value ~2 months after birth for lamivudine and ~3 months after birth for abacavir, with both drugs being fully mature ~2 years of age.

Table 1: Patient characteristics, n (%) or median (IQR) [Note: Abacavir group is the same as lamivudine group minus 2 children in both MDR-TB and control groups (n=54 total)]

	Lamivudine		Abacavir	
	MDR-TB (n=27)	Control (n=27)	MDR-TB (n=25)	Control (n=25)
Age (yr)	4.2 (1.6-9.6)	5.7 (1.6-9.5)	2.9 (1.4-9.4)	5.8 (2.7-9.6)
Males	12 (44)	13 (48)	11 (44)	12 (48)
Weight (kg)	13.4 (9.1-21.4)	15.6 (11.2-23.1)	13.2 (9.0-21.1)	16.3 (11.5-23.3)
Black ethnicity	24 (89)	14 (52)	22 (88)	12 (48)
Z-score of <-2 ^a				
Wt-for-age	16 (59)	9 (33)	16 (64)	8 (32)
Length-for-age	16 (59)	10 (37)	16 (64)	9 (36)
CD4 ⁺ T-cell count (cells/ μ l) ^b	549.5 (337.8-1210)	1026 (637-1535)	549.5 (326.8-1184)	1026 (710-1512.5)
Viral load (copies/ml) ^b	24375 (509-925557)	LDL ^c (LDL-1170)	12535 (381-945989)	LDL ^c (LDL-1044)
Clinical Stage 4	10 (37)	1 (4)	10 (40)	
Nasogastric tube	12 (44)	8 (30)	11 (44)	6 (24)
Formulation				
Suspension	18 (67)	10 (37)	21 (84)	11 (44)
Whole tablets	7 (26)	14 (52)	4 (16)	11 (44)
Crushed tablets	2 (7)	3 (11)		3 (12)
Antiretroviral treatment				
Lopinavir/ritonavir	16 (59)	16 (59)	15 (60)	14 (56)
Efavirenz	11 (41)	11 (41)	10 (40)	11 (44)
Antituberculosis treatment				
Pyrazinamide	27 (100)		25 (100)	
Terizidone	26 (96)		24 (96)	
Ethambutol	25 (93)		23 (92)	
Ethionamide	25 (93)		23 (92)	
High-dose isoniazid	24 (89)		22 (88)	
Amikacin	23 (85)		22 (88)	
Levofloxacin	9 (33)		9 (36)	
Ofloxacin	9 (33)		8 (32)	
Moxifloxacin	7 (26)		6 (24)	
Para-aminosalicylic acid	5 (19)		4 (16)	
Rifampicin ^d	4 (15)		4 (16)	
Linezolid	2 (7)		2 (8)	
Clofazimine	2 (7)		2 (8)	
Capreomycin	1 (4)		1 (4)	

^aWeight- and height-for-age Z-scores of <-2 include underweight/stunted to severely underweight/stunted participants.

^bMost recent routine result within 6 months of the pharmacokinetic sampling day. Seven participants for the CD4⁺ T-cell counts and 6 participants for viral load have been excluded from the analysis.

^cLDL: Lower than detectable limit < 50 copies/ml.

^dOf the participants receiving rifampicin, 3 where on an efavirenz-based regimen and 1 on a lopinavir/ritonavir-based regimen with super-boosted ritonavir.

Table 2. Parameter estimates of the final models

Parameters	Lamivudine		Abacavir	
	Typical value	BSV */ BOV (%)	Typical value	BSV */ BOV (%)
CL (L/h) ^a	10.8	14.7*	16.3	17.7*
V _c (L) ^a	26.5		21.7	
k _a (1/h)	1.07	66.0	1.77	74.5
MTT – suspension (h)	0.345	77.4	0.0834	119
MTT – tablets (h)	0.644		0.458	
NN ()	6.39		3.70	
F ()	1 (fixed)	29.4	1 (fixed)	48.9
Q (L/h) ^a	2.25		1.42	
V _p (L) ^a	69.7		12.0	
γ (shape of maturation) ^b	3.32		3.94	
PMAGE ₅₀ (months from conception) ^b	10.2		11.9	
Additive error (mg/L)	0.0048 (fixed) ^d		0.0048 (fixed) ^d	
Proportional error (%)	1.11		19.2	

^aCL, V, Q and V_p are scaled to a 15 kg child.

^bBayesian prior with values from Bouazza et al (7) for lamivudine and Tikiso et al (8) for abacavir were used for the estimation of maturation. PMAGE₅₀ is the postmenstrual age at which 50% of the maturation is reached.

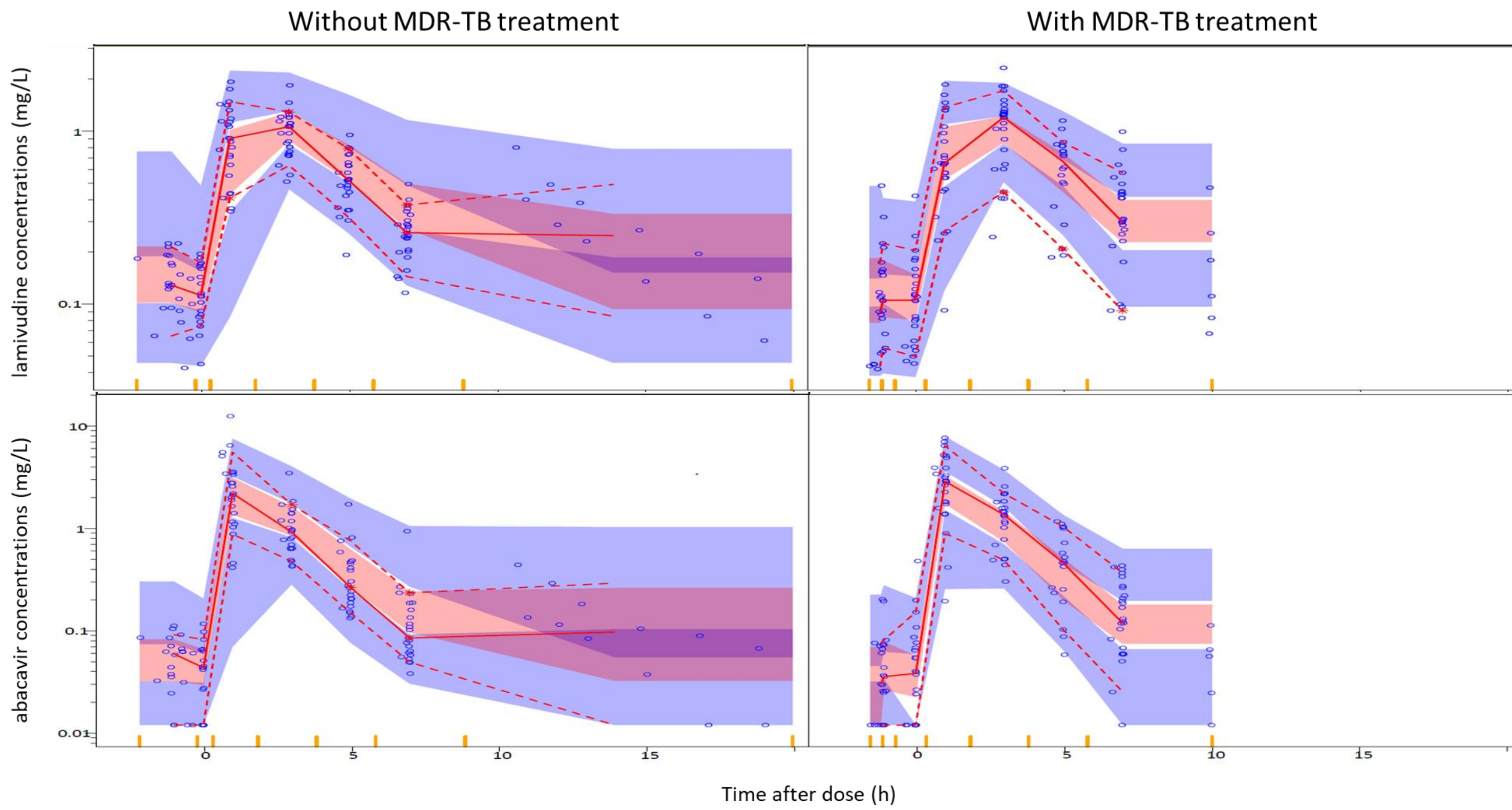


Figure 1. Visual predictive check. Lines represent the 5th, 50th, and 95th percentiles of observed data, shaded areas are the model-predicted 95% confidence intervals for the same percentiles.

- The absorption was faster with the suspension formulation than for the tablet for both drugs, but no effect was found on bioavailability.
- **No significant effect on bioavailability (F), CL, or absorption rate constants (ka) of lamivudine or abacavir was found for the drugs in this MDR-TB regimen.**

Conclusions

- **No significant effect was found on key pharmacokinetic parameters of lamivudine or abacavir when co-administered with routine drugs used for MDR-TB.**
- Lamivudine and abacavir suspension had significantly faster absorption compared to tablets.

While these findings need to be considered in the context of the modest sample size, they are reassuring and suggest the absence of major DDIs between lamivudine, abacavir and the MDR-TB drugs in our study. DDIs require further studies in newer MDR-TB drugs including bedaquiline, delamanid and linezolid, in HIV-infected children.

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