Pharmacokinetics of antiretroviral and tuberculosis drugs in children with HIV/TB co-infection: a systematic review

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Introduction: Management of concomitant use of ART and TB drugs is difficult because of the many drug–drug interactions (DDIs) between the medications. This systematic review provides an overview of the current state of knowledge about the pharmacokinetics (PK) of ART and TB treatment in children with HIV/TB co-infection, and identifies knowledge gaps.

Methods: We searched Embase and PubMed, and systematically searched abstract books of relevant conferences, following PRISMA guidelines. Studies not reporting PK parameters, investigating medicines that are not available any longer or not including children with HIV/TB co-infection were excluded. All studies were assessed for quality.

Results: In total, 47 studies met the inclusion criteria. No dose adjustments are necessary for efavirenz during concomitant first-line TB treatment use, but intersubject PK variability was high, especially in children <3 years of age. Super-boosted lopinavir/ritonavir (ratio 1:1) resulted in adequate lopinavir trough concentrations during rifampicin co-administration. Double-dosed raltegravir can be given with rifampicin in children >4 weeks old as well as twice-daily dolutegravir (instead of once daily) in children older than 6 years. Exposure to some TB drugs (ethambutol and rifampicin) was reduced in the setting of HIV infection, regardless of ART use. Only limited PK data of second-line TB drugs with ART in children who are HIV infected have been published.

Conclusions: Whereas integrase inhibitors seem favourable in older children, there are limited options for ART in young children (<3 years) receiving rifampicin-based TB therapy. The PK of TB drugs in HIV-infected children warrants further research.

Introduction

Currently, TB is the leading cause of death from a single infectious agent, followed by HIV.1,2 In 2018, approximately 1.7 million children <15 years old were living with HIV, of whom 100,000 died.3 Mortality amongst HIV-infected children has dramatically decreased worldwide with the introduction of combination ART.3,4 However, only half of children aged <15 years needing ART are estimated to be receiving it.5 TB is the single largest cause of death among HIV-infected patients.2 The WHO estimated that 1.1 million children developed TB in 2018 and 205,000 children died from TB disease, including 32,000 children with HIV.2 The incidence of TB has decreased6 and TB treatment outcome has improved7...
amongst HIV-infected children since the introduction of paediatric ART. About 23% of the global population has latent TB infection (LTBI), of whom about 5%–10% eventually develop TB with increased risk in children and people living with HIV. Both ART and LTBI treatment reduce TB incidence in adults, but the benefit of LTBI treatment in HIV-infected children is unclear.

Children living with HIV are eight times more likely to develop TB in moderate and high endemic areas for TB compared with HIV-uninfected children. Even when on successful ART, TB is an important cause of illness in HIV-infected patients. Both infections negatively influence progression and treatment outcome of the other infection. Therefore, effective treatment strategies and treatment optimization are needed to achieve control of both HIV and TB simultaneously. However, management of concomitant use of ART and TB treatment is challenging because of adherence issues, overlapping toxicities, risk of immune reconstitution inflammatory syndrome and drug–drug interactions (DDIs).

Dose recommendations for paediatric ART are often based on small studies, but paediatric ART dose optimization is becoming increasingly important in drug development. There are, however, still many knowledge gaps concerning ART in children receiving concomitant TB treatment, and vice versa. First-line treatment of drug-susceptible TB in children consists of isoniazid, rifampicin, pyrazinamide and ethambutol for 2 months, followed by isoniazid and rifampicin for 4 months. These medicines have been used in children for more than 40 years, initially at mg/kg doses similar to those in adults. However, exposure to (adult-dosed) TB drugs in paediatric pharmacokinetic (PK) studies was low compared with that in adults. Hence, since 2010, higher mg/kg doses are recommended for children. Rifabutin is also used for treatment of adult TB, but it is rarely used in children due to minimal paediatric clinical data, few paediatric formulations, limited global availability and high prices. Rifapentine (RPT) has recently been registered for children down to 2 years old for treatment of LTBI. However, it is also not used frequently in children due to availability issues and high prices.

Paediatric dose recommendations for some drugs used for MDR-TB and HIV have only been established recently. Therefore, PK assessments of various MDR-TB drugs and new antiretrovirals (ARVs) have not yet been done in children with HIV-associated TB.

HIV and TB drug PK parameters are significant determinants of clinical response to treatment. Efficacy of most ARVs is related to trough plasma concentration (C_{trough}) and to a lesser extent to AUC, whereas for TB treatment efficacy relates mostly to AUC and C_{max}. PK targets for children and correlation with efficacy and toxicity are generally extrapolated from adult data. For TB treatment in children with HIV, low C_{max} values of rifampicin and pyrazinamide are associated with TB treatment failure. There are many DDIs between ART and TB treatment; the most clinically significant is due to induction of many enzyme systems (see Figure 1) responsible for metabolism of ARVs by rifampicin.

Frequently, dose adjustments are needed to overcome DDIs, or patients are switched to other ARVs when TB drugs are used concomitantly. On the other hand, PK of TB drugs can be altered in patients with HIV. Examples are effects of efavirenz on bedaquiline and moxifloxacin PK through enzyme induction, or lower exposure to TB drugs due to malabsorption that is believed to be caused by malnutrition, diarrhoea or infections in children with HIV. Dose recommendations for management of DDIs in children are often extrapolated from adults. Differences in children’s physiology, such as plasma protein binding, maturation of metabolizing enzymes and development of renal function, compared with adults can however affect drug exposure in the body and may also change the magnitude of DDIs. Therefore, it is of utmost importance to conduct PK interaction studies in children to evaluate proposed dosing regimens in children who are HIV/TB co-infected.

This systematic review aims to identify all literature about PK of ART and TB treatment with currently available drugs in children with HIV-associated TB, evaluate PK parameters in these studies in comparison with adult data and create an overview of the current state of knowledge. Moreover, we want to identify knowledge gaps and explore future challenges and opportunities in HIV/TB PK research in children.
**Figure 1.** Metabolic pathways and inducing/inhibitory potential of antiretroviral and TB drugs. X = metabolic pathway; X(M) = main metabolic pathway; green box = induction; red box = inhibition; yellow box = both induction and inhibition; X(U) = other hepatic metabolic pathway or unknown metabolic pathway. This figure appears in colour in the online version of JAC and in black and white in the print version of JAC.
assessed the PK of TB treatment, 8 of MDR-TB treatment and one assessed the PK of a first-line TB drug used for LTBI treatment. All study characteristics as well as quality assessments of the studies are reported in Table 1 (DDIs) and Table 2 (PK of first-line TB drugs in children with HIV/TB co-infection). Information about the mechanism of interaction and PK data in adults is shown to compare the DDI effect size in children with that in adults.

Effects of TB drugs on ART

Drugs used for TB treatment affect PK parameters of many ARVs. Rifampicin is a strong inducer of cytochrome P450 (CYP)2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A4, UDP-glucuronosyltransferase (UGT) and P-glycoprotein (P-gp).32 The induction potential of rifapentine is slightly less than or comparable to that of rifampicin. Very few studies have directly assessed differences in DDI magnitude between ART and rifapentine or rifampicin.33,34 Rifabutin is known to be a less potent CYP inducer compared with rifampicin and rifapentine.35 Isoniazid is known to inhibit CYP2C9, CYP2C19, and CYP2E1 and CYP3A4 to some extent,36 but the inhibiting effect of isoniazid is outweighed by the strong inducing effect of rifampicin when both are used in combination. Rifampicin and rifabutin are mainly used for treatment of TB, whereas rifapentine is predominantly used for LTBI treatment, and isoniazid is used for both treatments. The effects of TB treatment (perpetrator drugs) on ARVs (victim drugs) in children are described below.

Integrase strand transfer inhibitors

A dolutegravir-based ART regimen has recently been included in the WHO guidelines as the preferred first-line regimen in children weighing >20 kg.37 Dolutegravir is primarily metabolized by UGT1A1 and to some extent by CYP3A, while rifampicin strongly induces those enzymes,32 leading to lower dolutegravir exposure in adults (AUC0–tau $\geq$ 54%; Ctrough $\geq$ 72%).38 It has been shown in adults receiving rifampicin that increasing dolutegravir dose to 50 mg twice daily (q12h) is safe and results in a similar exposure compared with dolutegravir 50 mg once daily (q24h) without rifampicin (AUC0–24h $\leq$ 33%; Ctrough $\leq$ 22%).38,39 Co-administration of dolutegravir q12h and rifampicin has been investigated in 13 children 6–18 years old with HIV and TB, receiving either 25 mg or 50 mg dolutegravir q12h. An intrasubject comparison of dolutegravir PK parameters on TB treatment (q12h dolutegravir dosing) with dolutegravir PK parameters after stopping TB treatment (with rifampicin) showed that the AUC0–24h was similar for both situations. Moreover, while on dolutegravir q12h with rifampicin, all children had therapeutic Ctrough, and no safety issues in this study were related to dolutegravir.40 Twice-daily dolutegravir dosing in children >6 years old, following the 2019 WHO dose recommendation for children, is assumed to be safe and sufficient to attenuate the interaction with rifampicin. More research is needed to strengthen these results and evaluate the strategy in younger children and when the adult dose of 50 mg dolutegravir is given to children of 20–25 kg.

Raltegravir is predominantly metabolized by UGT1A1. PK data of raltegravir seem different in HIV/TB-co-infected adults
Table 1. Characteristics of studies investigating DDIs between ARVs and TB drugs

| Reference                  | Study design                          | No. of subjects (co-infected) | Age of subjects (IQR/range/SD as reported) | PK drug; dose PK parameters | Without perpetrator (IQR/range/SD as reported) | With perpetrator (IQR/range/SD as reported) | Effect (P value) | Conclusion | Quality of evidence |
|----------------------------|---------------------------------------|------------------------------|-------------------------------------------|-----------------------------|-----------------------------------------------|---------------------------------------------|-------------------|-------------|---------------------|
| **Protease inhibitors**    |                                       |                              |                                           |                             |                                               |                                             |                   |             |                     |
| Archary, M. et al. (2018)  | PopPK evaluating LPV PK in malnourished children with HIV versus peers with HIV/TB on super-boosted LPV/r + RIF-ATT | 62 [20 (10 early start, 10 late)] | Mean (SD): Early: 15.5 months (16.3) Delayed: 14.5 months (10.8) | LPV/r, WHO weight band dosage ATT as covariate in LPV PK model | NR                                           | NR                                          | NS                | Super-boosted LPV/r in HIV/TB-infected malnourished children resulted in similar LPV exposure compared with children without ATT | Low               |
| Elsherbiny, D. et al. (2010) | PopPK evaluating LPV PK in children with HIV versus peers with HIV/TB on super-boosted LPV/r + RIF-ATT | 30 (15) + intrasubject | 0.57–4.23 years No TB 9–47 months; TB 7–34 months | Relative clearance (L/h) | 0.9                                           | 1.26                                        | +40%              | Super-boosted LPV/r with RIF resulted in a slight increase in clearance, but with adequate predicted Ctrough values | Moderate           |
| McIlleron H. et al. (2011) | NCA PK evaluating LPV PK in children with HIV versus peers with HIV/TB on double-dosed LPV/r + RIF-ATT | 44 (20) | Median (IQR): HIV/TB: 1.23 years (0.98–1.93) HIV: 1.59 years (1.15–2.23) | LPV/r q12h 230/57.5 mg/m² (double dose) | AUC₂₄ₙₐₜ (mg h/L) Cmax (mg/L) Ctrough <1.0 mg/L (%) | 49.2 (40.7–86.6) 7.9 (6.9–13.4) 4.2 (4.3–8.1) 8% | 23.9 (13.8–49.6) 4.5 (2.5–8.2) 0.7 (0.1–2.0) 60% | –51.4% (<0.001) Double-dosed LPV/r resulted in inadequate lopinavir concentrations in young children treated concurrently with rifampicin | High              |
| Rabie, H. et al. (2019)    | PopPK evaluating LPV PK in children with HIV/TB on super-boosted LPV/r + RIF-ATT and off ATT | 96 (96) (intrasubject) | 18.2 months (9.6–26.8) | Relative clearance (L/h) | 8.8% (95% CI 0.6–19.8) | 7.6% (0.4–16.2) NS | Super-boosted LPV/r during RIF-based ATT was non-inferior to the exposure LPV/r without rifampicin | High              |
| Rabie, H. et al. (2019)    | NCA PK evaluating LPV PK in children with HIV/TB on 8-hourly LPV/r + RIF-ATT | 11 (11) | Median (IQR): HIV/TB: 15 months (12.6–28.8) | LPV/r, WHO weight band dosage q12h or TDS | Median (IQR): AUC₂₄ₙₐₜ, LPV AUC₂₄ₙₐₜ, RTV (mg h/L) Cmax, LPV Cmax, RTV (mg/L) Ctrough, LPV Ctrough, RTV (mg/L) (%) | – 48.7 (46.7–72.7) – 2.09 (0.4–1.3–3.4) – 7.3 (2.0–13.4) – 0.39 (0.07–0.81) – 3 (0.1–1.5) – 0.11 (0.02–0.22) 36% 45% | 117.8 (80.4–176.1) 14.2 (11.9–23.5) 4.64 (2.32–10.40) 0% 13% | –31.3% (0.036) These PK parameters do not support the use of an 8-hourly dosing regimen for LPV/r in children using RIF-based ATT | Low               |
| Ren, Y. et al. (2008)      | NCA PK evaluating LPV PK in children with HIV versus peers with HIV/TB on super-boosted LPV/r + RIF-ATT | 30 (15) | Median (IQR): HIV/TB: 16 months (14–24) HIV: 29 months (22–34) | LPV/r, WHO weight band dosage q12h or 4× higher RTV | Median (IQR): AUC₂₄ₙₐₜ, (mg h/L) Cmax, LPV Ctrough, LPV (mg/L) (%) | 117.8 (80.4–176.1) 14.2 (11.9–23.5) 4.64 (2.32–10.40) 0% 13% | 80.9 (50.9–121.7) 10.5 (7.1–14.3) 3.94 (2.26–7.66) 13% | –31.3% (0.036) Super-boosted LPV/r was sufficient to overcome the effect of RIF-based ATT | High              |

Continued
| Reference                        | Study design                                           | No. of subjects (co-infected) | Age of subjects (IQR/range/SD as reported) | PK drug; dose | PK parameters | Without perpetrator PK drug; dose PK parameters | With perpetrator PK drug; dose PK parameters | Effect (P value) | Conclusion                                                                 |
|---------------------------------|--------------------------------------------------------|------------------------------|--------------------------------------------|---------------|---------------|------------------------------------------------|---------------------------------------------|----------------|----------------------------------------------------------------------------|
| van der Laan, L. E. et al. (2018) | PopPK assessing effects of INH/PZA/EMB/ETH/TRD/FQ/AMK on LPV/r PK in children with HIV/MDR-TB, including 2 children on super-boosted LPV/r and RIF | 32 (16)                       | Median (IQR): HIV/TB: 1.9 years (1.0–2.7) HIV: 2.2 years (0.7–5.3) | LPV/r 300/75 mg/m² or LPV 300/300 mg/m² + RIF (n=2) | Predicted median LPV C₃₀₋₅₀₀ (mg/L) C₃₀₋₅₀₀ <1.0 mg/L (%) | 6.5 12%                              | 5.7 19%                | NS                  | Co-administration of LPV/r with MDR-TB drugs did not significantly affect key PK parameters of LPV/r | Low |
| Zhang, C. et al. (2012)         | PopPK to predict LPV/r dose to achieve target LPV exposure in children on LPV/r + RIF | 74 (24) + 11 intrasubject     | Median (range): 21 months (6 months–4.5 years) | LPV control: 11.6 mg/kg (9.4–11.0) LPV super-boosted: 14.0 mg/kg (10.7–18.0) LPV double dose: 23.0 mg/kg (13.8–29.5) | Predicted LPV/r dose to have C₃₀₋₅₀₀ >1 mg/l in >95% of children weighing 3–5.9 kg | – | Super-boosted (SB): 22/22 mg/kg Double dosed (DD): 52/13 mg/kg 8-hourly dose (8-h): 27/6.75 mg/kg | – | Smaller children need higher LPV/r doses when receiving RIF-ATT. 8-hourly dosing of LPV/r could be beneficial in HIV/TB-co-infected children. | Low |
| Rabie, H. et al. (2020)         | PopPK to evaluate differences in children versus adults in LPV/r exposure in patients on LPV/r + RIF-ATT | 74 (24) + 11 intrasubject     | Median: 21 months (6 months–4.5 years) | Median LPV/r 12.0/2.9 mg/kg (range 9.2–16.0/2.3–4.6) In absence of RIF | Difference in LPV clearance (%) | NR | Child: +48% Adult: +58% | – | This model characterized differences between adults and children in the effect of RIF on the PK of LPV/r with lopinavir and ritonavir. | Low |
| Rabie, H. et al. (2020)         | PopPK to evaluate differences in ABC PK in children with HIV/TB on ABC versus ABC + RIF-ATT | 87 (87; intrasubject)         | Median (range): 2.8 years (0.25–6) | ABC, q12h South African weight band dosing recommendations LPV/r super-boosted in case of RIF | Decrease bioavailability and AUC (%) | NR | Child: –36% Adult: –25% | – | ABC exposure was decreased by concomitant administration of RIF and super-boosted LPV/r. | Moderate |
| Integrase strand transfer inhibitor | Study | No. | Median (range): | DTG, 25 mg or 50 mg q12h on ATT and q24h off ATT | GM (CV%) | AUC<sub>3</sub> (mg h/L) | C<sub>max</sub> (mg/L) | C<sub>av</sub> (mg/L) | Relative clearance (L/h) | Median (IQR): | Treatment effect | Notes |
|-----------------------------------|-------|-----|----------------|---------------------------------|----------|----------------------|-----------------|------------------|---------------------|----------------|-----------------|-------|
| Waalewijn, H. et al. (2020) 49    | NCA PK evaluating DTG PK in children with HIV/TB on DTG q12h + RIF-ATT versus DTG q24h after completing ATT | 13 (13; intrasubject) | Median (range): 12.3 years (6.8-16.1) | DTG, 25 mg or 50 mg q12h on ATT and q24h off ATT | GM (CV%) | AUC<sub>0,21</sub>, 25 mg (mg h/L) | C<sub>max</sub> 25 mg | C<sub>av</sub> 25 mg | Relative clearance (L/h) | 7.2 (7.1-8.3) | 7.0 years (5.0-9.2) | -8% 0% Very low |
| Meyers, T. et al. (2019) 65      | NCA PK evaluating RAL PK in children with HIV versus peers with HIV/TB on double-dosed RAL+RIF-ATT | 14 (14) | Median (range): 8 years (7–9) | RAL; 12 mg/kg q12h | GM (CV%) | AUC<sub>0,21</sub>, 12 mg (umol/L) | C<sub>max</sub> (nmol/L) | C<sub>av</sub> (nmol/L) | Relative clearance (L/h) | 17.2 (16.2-18.2) | 7.0 years (5.0–10.0) | Moderate |
| Krogstad, P. et al. (2020) 66    | NCA PK evaluating RAL PK in infants (6 weeks–2 years) with HIV versus peers with HIV/TB on double-dosed RAL + RIF-ATT | 13 (13) | Median: 1.2-4 months | RAL; 12 mg/kg q12h | GM (CV%) | AUC<sub>0,21</sub>, 12 mg (umol/L) | C<sub>max</sub> (nmol/L) | C<sub>av</sub> (nmol/L) | Relative clearance (L/h) | 106 (57%) | 7.0 years (5.0–10.0) | Moderate |
| Non-nucleoside reverse transcriptase inhibitor | Study | No. | Median (range): | Relative clearance (L/h) | Median (IQR): | Treatment effect | Notes |
| Alghamdi, W.A. et al. (2019) 82  | NCA PK evaluating aPK PK in children with HIV versus peers with HIV/TB on normal-dosed EFV + RIF/INH-TB | 105 (46) | Median (range): 7.1 years (3.0-14.2) | EFV; 2006 WHO-recommended dose | C<sub>av</sub> (mg/L) | 1<mg/L | 1-4 mg/L | >4 mg/L | Relative clearance (L/h) | 5.7 (5.3-6.1) | 4.0 (2.5-5.5) | Moderate |
| Bwakura Dangarembizi, M. et al. (2019) 86 | NCA PK evaluating EFV PK in children with HIV/TB <3 years on RIF/INH-TB and 30% increased EFV dose | 14 (14) | Median (IQR): 14.5 months (11-23) | EFV; 2006 WHO-recommended dose for HIV/TB | C<sub>av</sub> (mg/L) | <1 mg/L | 1-4 mg/L | >4 mg/L | Relative clearance (L/h) | 31% 23% | 46% | Very low |
| Ren, Y. et al. (2009) 60         | NCA PK evaluating EFV PK in children with HIV/TB on normal-dosed EFV+RIF/INH-TB versus after TB treatment | 15 (15) | Median: HIV/TB <6 years (4, 3-9.0) | EFV; 2006 WHO-recommended dose | C<sub>av</sub> (mg/L) | Subtherapeutic | C<sub>av</sub> (mg/L) | Relative clearance (L/h) | 0.86 (0.61-3.56) | 0.83 (0.59-6.57) | 53% | Very low |
| Kwara, A. et al. (2019) 83      | NCA PK evaluating EFV PK in children with HIV versus peers with HIV/TB on normal-dosed EFV+RIF/INH-TB | 105 (43) | Median (IQR): 15.0 mg/kg (13.7–16.9) | GM (95% CI): | AUC<sub>0,21</sub> (mg h/L) | C<sub>max</sub> (mg/L) | C<sub>av</sub> (mg/L) | Relative clearance (L/h) | Control: 60.9 (51.8-71.5) | On ATT: 56.4 (45.3-70.5) | NS (0.575) | Moderate |

Continued
| Reference                     | Study design                                                                 | No. of subjects (co-infected) | Age of subjects (IQR/range/SD as reported) | PK drug; dose | PK parameters | Without perpetrator (IQR/Range/SD as reported) | With perpetrator (IQR/Range/SD as reported) | Effect (P value) | Conclusion                                                                                      | Quality of evidence |
|-------------------------------|-------------------------------------------------------------------------------|-------------------------------|---------------------------------------------|---------------|--------------|------------------------------------------------|--------------------------------------------|------------------|-------------------------------------------------------------------------------|-------------------|
| McIlleron, H. M. et al. (2013) | PopPK evaluating impact of genotype on differences in EFV PK in children with HIV/TB on RIF/INH-ATT versus after completing ATT | 81 (40) + 23 intra-subject    | Median (IQR): TB: 7.5 years (6.4–10.9) After TB: 8.5 years (5.0–11.3) Control: 8.1 years (6.4–9.6) | EFV; WHO-recommended dose | Increase EFV mid-dose concentration -Slow metabolizers -Intermediate -Fast | Control: 1.9 (1.6–2.3) TB IP: 1.19 (0.76–1.86) NR | On ATT: 1.5 (1.0–2.1) TB IP: 1.50 (0.93–2.41) NR | NS (0.230) NS (0.332) | 1.49-fold (95% CI 1.10–2.01) | Moderate |
| Shah, I. et al. (2011) | NCA PK evaluating NVP and EFV PK in children with HIV/TB while increasing NVP dose by 20–30% or normal-dosed EFV when on RIF-ATT versus after TB treatment. | 29 (3) | Mean (SD): 8.1 (3.3) years | LPV; WHO weight band dosage | | | | | | | Very low |
| Enimil A. et al. (2019) | NCA PK evaluating NVP PK in children with HIV versus peers with HIV/TB on normal-dosed NVP + RIF/INH-TB | 53 (23) + 16 intra-subject    | Median (IQR): 1.6 years (1.1–2.0) | NVP; according to WHO guidelines | | | | | | | Very low |
| McIlleron, H. et al. (2017) | PopPK evaluating NVP PK in children with HIV versus HIV/TB on normal- | 164 (468) | Range: 2–83 days | NVP; various (depending on birth weight) | | | | | | | Low |

**Table 1. Continued**
| Study | Design | Participants | Methods | Findings |
|-------|--------|--------------|---------|----------|
| Oudijk, J. M. et al. (2012) | NCA PK evaluating NVP PK in children with HIV versus peers with HIV/TB on normal-dosed NVP + RIF-ATT | 21 (21) + 16 external controls | Median (range): 1.6 years (0.7–3.2) | C\text{trough} (mg/L) ≥28 days after birth Overall C\text{trough} difference (%) Median (range) \text{AUC}_{0-24h} (mg h/L) C_{\text{max}} (mg/L) C_{\text{trough}} (mg/L) C_{\text{trough}} <3.0 mg/L (%) 1.39 (1.01, 1.98) NR 90.9 (40.4–232.1) 9.59 (5.28–21.04) 5.93 (3.28–18.13) 0% 0.89 (0.60, 1.57) – 52.0 (22.6–159.7) 6.33 (2.61–14.5) 2.93 (1.06–11.4) –33% (<0.01) –34% (<0.001) 52% (0.001) |
| Prasitsuebsai, W. et al. (2012) | NCA PK evaluating NVP PK in children with HIV/TB on 12% higher dosed NVP + RIF -ATT versus after TB treatment | 8 (8) + 6 intrasubject | Median (range): 9.7 years (4.4–11.7) | C\text{trough} (mg/L) \text{AUC}_{0-24h} (mg h/L) C_{\text{max}} (mg/L) C_{\text{trough}} <3.0 mg/L (%) 70.8 (range: 5.6–19.5) 5.20 (range: 3.78–7.32) 4.2 (0.83–16.0) 0.385 (0.19–0.46) –6.91 (3.52–8.67) – 2.24 – 0.14 – |
| Barlow-Mosha, L. et al. (2009) | NCA PK evaluating NVP PK in children with HIV/TB using NVP + RIF-ATT | 20 (7) | Median (range): 5.0 years (1.2–11.3) | C\text{trough} (mg/L) \text{AUC}_{0-24h} (mg h/L) C_{\text{max}} (mg/L) \text{C\text{trough}} <3.0 mg/L (%) 4.2 (0.83–16.0) NR 0% 2.9 (1.7–10.0) 57% 0% |
| TB treatment | | | | Children were receiving a significantly higher nevirapine dose while receiving rifampicin. The results support WHO dosing recommendations. Very low |
| Moultrie, H. et al. (2015) | NCA PK evaluating RFB PK in HIV+/TB children using LPV/r | 6 (6) | Range: 10–41 months | RFB 5 mg/kg 3x week | Median \text{AUC}_{0-4h} (\mu g h/mL) Median C_{\text{max}} (mg/L) \text{C\text{trough}} (mg/L) \text{AUC}_{0-24h} (l g/h/mL) \text{RFB} 1 DD 2.5 mg/kg RFB AUC_{0-24h} (l g/h/mL) \text{RFB} 1 DD 2.5 mg/kg \text{RFB}_{\text{C\text{max}}} (mg/L) \text{RFB} 2.5 mg/kg daily achieved \text{AUC}_{0-24h} comparable to adults in children receiving both LPV/r and RFB. Moderate |
| Rawizza, H. E. et al. (2018) | NCA PK evaluating RFB and 25-O-desacetyl RFB PK in HIV/TB co-infected children using LPV/r | 8 (8) | Median: 13.5 (12.8–14.3) | RFB 1 DD 2.5 mg/kg | \text{RFB}_{\text{AUC}_{0-24h}} (\mu g h/mL) \text{RFB}_{\text{C\text{max}}} (mg/L) 25-O \text{AUC}_{0-24h} (\mu g h/mL) 25-O \text{C\text{max}} (mg/L) 4.77 – 0.4 – 0.14 – |

ABC, abacavir; AMK, amikacin; ATT, antituberculosis treatment; DTG, dolutegravir; EMB, ethambutol; ETH, ethionamide; EFV, efavirenz; FQ, fluoroquinolone; INH, isoniazid; LVX, levofloxacin; LZD, linezolid; LPV, lopinavir; LPV/r, lopinavir/ritonavir; MXF, moxifloxacin; NCA, non-compartmental analysis; NR, not reported; NVP, nevirapine; PK, pharmacokinetic; PK-PD, pharmacokinetics–pharmacodynamics; popPK, population pharmacokinetics; PZA, pyrazinamide; RAL, raltegravir; RIF, rifampicin; RIF-ATT, rifampicin-containing tuberculosis treatment; RIF/INH-TB, rifampicin + isoniazid-containing tuberculosis treatment; RTV, ritonavir; TDS, thrice daily; TIW, thrice weekly; TRD, terizidone.

a Conference abstract.

b Infants born to mothers with TB.
| Reference | Study design | No. of subjects (co-infected; on ART at enrolment) | Age of subjects (IQR/range/SD as reported) | PK drug; dose (IQR/range/SD as reported) | PK parameters | TB monoinfection (IQR/range/SD as reported) | HIV/TB co-infection (IQR/range/SD as reported) | Effect (P value) | Conclusion | Quality of evidence |
|-----------|--------------|------------------------------------------------|------------------------------------------|---------------------------------------------|---------------|------------------------------------------|-----------------------------------------------|----------------|-------------|---------------------|
| **First-line TB treatment** | | | | | | | | | | |
| Antwi, S. et al. (2017) | NCA PK evaluating INH/RIF/PRZ/EMB PK in children with HIV versus without HIV | 113 (59; 0) | Median (IQR): 5.0 years (2.2–8.3) | INH q24h median (IQR): 1.12 mg/kg (9.1–12.8) | Median (IQR): AUC<sub>0–24</sub> (µg h/mL): 21.15 (16.48–25.92) | Mean (SD): 18.37 (12.20–26.90) | NS (0.231) | PK parameters of RIF, PZA and EMB were adversely affected by HIV co-infection. | Moderate |
| Bekker, A. et al. (2016) | NCA PK evaluating INH/RIF/PRZ/EMB PK in children with HIV versus without HIV | 39 (5; 5) | Mean (SD): 6.6 months (3.0) | INH mean (range) q24h: 1.38 mg/kg (9.0–19.7) | Mean (SD): 11.48 (8.66) | Mean (SD): 16.46 (15.0) | NS (0.283) | Lower PZA and EMB exposures in HIV-infected infants were observed; however, only 5 HIV-coinfected infants were studied. | Low |
| Graham, S. M. et al. (2006) | NCA PK evaluating PRZ/EMB PK in children with HIV versus without HIV on thrice-weekly TB regimen | PZA 27 (18; 0) | Mean (range): 5.7 years (0.9–14) | Mean (SD): 322 (240) | Mean (SD): 411 (382) | NS | No significant differences on PZA and EMB exposure in HIV-infected children were found. Overall low PK parameters suggest need for dose increase. | Very low |
| Guastrennec, B. et al. (2018) | PK–PD analysis assessing impact of HIV infection on INH/RIF/PRZ PK and TB treatment outcome | EMB 18 (6; 0) | Mean (range): 5.5 years (1–12) | AUC<sub>0–24</sub> (µg h/mL): 4.19 (2.29) | AUC<sub>24–48</sub> (µg h/mL): 34.0 (18.1) | NS | HIV/TB co-infection was related to lower INH and RIF levels rather than usage of ART. | Low |
| Kwarar, A. et al. (2016) | NCA PK evaluating INH/RIF/PRZ/EMB PK in children with HIV versus without HIV | 62 (28; NR) | Median (IQR): 5.0 years (2.8–8.9) | INH q24h median (IQR): 11.11 mg/kg (9.0–13.2) | Median (IQR): AUC<sub>0–24</sub> (µg h/mL): 19.4 (13.4–25.9) | Mean (SD): 14.3 (9.1–20.0) | NS (0.060) | High prevalence of low RIF and EMB concentrations was shown in Ghanaian children with TB despite receiving revised WHO dosages. Moreover, HIV infection was an | Moderate |
### Mukherjee, A. et al. (2016) 148

NCA PK evaluating INH/RIF/PR/Z/EMB PK in children with HIV versus without HIV

| Medication | Mean (SD): HIV/ TB 105.9 months (43.1) TB 97.2 months (43.9) | Mean (range): INH 5.7 mg/kg (5–7.3) | Plasma concentrations of EMB were lower in HIV-infected children compared with HIV-uninfected children. |
|------------|-----------------------------------------------------------|-------------------------------------|-------------------------------------------------|
| EMB q24h 18.4 mg/kg (15.8–22.0) | C_{\text{max}} (mg/L) 30.4 (25.0–35.4) | 23.2 (19.2–36.5) | NS (0.289) |
|            | C_{\text{max}} (\mu g/mL) 8.1 (5.3–11.0) | 4.9 (3.4–7.6) | –41% (0.019) |
|            | C_{\text{min}} (mg/L) 2.4 (1.5–3.3) | 1.1 (0.7–2.4) | –54% (0.011) |
|            | (95% CI) 1.31 (0.77–2.22) | 2.04 (1.53–2.74) | NS |
|            | AUC_{0–4h} (l/h/mL) 0.58 (0.35–0.97) | 0.99 (0.73–1.34) | NS |

### Ramachandran, G. et al. (2016) 26

NCA PK evaluating INH/RIF/PR/Z/EMB PK and treatment outcome in children with HIV versus without HIV

| Medication | Median (IQR): HIV/TB 9.0 years (6.5–11.0) TB 7.0 years (4.0–10.0) | Mean: HIV/TB 54 (21;0) Median (IQR) 3.73 years (4.0–5.6) | High |
|------------|-----------------------------------------------------------|-----------------------------------------------|-------------------------------------------------|
| INH q24h 10 mg/kg (20–29.6) | C_{\text{max}} (mg/L) 22.0 (15.0–33.1) | 19.9 (10.7–30.8) | NS (0.056) |
|            | C_{\text{max}} (\mu g/mL) 6.1 (4.0–8.4) | 4.7 (2.8–7.2) | –23% (0.008) |
|            | (95% CI) 5.1 (3.4–6.9) | 2.6 (1.3–4.5) | +57% (0.012) |
|            | AUC_{0–4h} (l/h/mL) 12% | 28% | NS |
| RIF q24h 10 mg/kg | AUC_{0–4h} (\mu g/mL) 23.4 (15.1–33.2) | 10.4 (6.1–18.2) | NS (0.001) |
|            | C_{\text{max}} (mg/L) 5.1 | 2.6 | –49% (0.001) |
|            | C_{\text{max}} (\mu g/mL) 92% | 97% | NS (0.12) |
| PZA q24h 32.6 mg/kg | AUC_{0–4h} (\mu g/mL) 218.2 (175.9–255.8) | 219.1 (172.6–273.9) | NS (0.452) |
|            | C_{\text{max}} (mg/L) 39.2 | 41.2 | NS (0.132) |
|            | C_{\text{max}} (\mu g/mL) (30.5–44.9) | (31.7–48.0) | NR |
|            | AUC_{0–4h} (l/h/mL) NR | NR | NS (0.12) |

### Schaaf, H. S. et al. (2009) 18

NCA PK evaluating RIF PK in children with HIV versus without HIV

| Medication | Mean: HIV/TB 54 (21;0) 3.73 years (4.0–5.6) | Mean: HIV/TB 54 (21;0) 3.73 years (4.0–5.6) | Low |
|------------|------------------------------------------------|------------------------------------------------|------------------------------------------------|
| RIF q24h 9.61 mg/kg (6.47–5.58) | AUC_{0–4h} (\mu g/mL) 18.07 (12.52) | 17.94 (10.36) | NS (0.59) |
| RIF q24h 9.63 mg/kg (4.6–17.8) at 4 months | AUC_{0–4h} (\mu g/mL) 18.07 (12.52) | 17.94 (10.36) | NS (0.59) |
|            | C_{\text{max}} (mg/L) 6.92 | 6.28 (5.88) | 6.26 (3.41) | 4.91 (2.03) | 5.67 (3.30) | 4.91 (2.03) | 5.67 (3.30) | NS (0.08) |
|            | C_{\text{max}} (\mu g/mL) 15 (9.2) | 14.88 (7.43) | 16.52 (8.84) | NS (0.25) |
|            | C_{\text{min}} (mg/L) NR | NR | NR | NS (0.53) |

### Thee, S. et al. (2011) 147

NCA PK evaluating INH/RIF/PR/Z/EMB PK in children with HIV versus without HIV <2 years

| Medication | Mean: HIV/TB 20 (5; 5) | Mean: HIV/TB 20 (5; 5) | Very Low |
|------------|------------------------------------------------|------------------------------------------------|------------------------------------------------|
| INH q24h 10 mg/kg (10–15) LD5/HD10 | AUC_{0–4h} (\mu g/mL) 7.39 (4.98–9.80) | 10.21 (1.98–14.64) | NS (0.413) |
|            | C_{\text{max}} (mg/L) 19.54 | 22.81 (10.19–35.42) | NS (0.552) |
|            | C_{\text{min}} (\mu g/mL) 3.19 | 3.20 (1.25–5.15) | NS (0.909) |
|            | AUC_{0–4h} (l/h/mL) 8.50 | 6.91 (4.37–9.46) | NS (0.292) |
| RIF q24h 15 mg/kg (10–20) LD10/HD15 | AUC_{0–4h} (\mu g/mL) 18.61 (12.80–24.02) | 16.68 (10.24–33.12) | NS (0.774) |
|            | C_{\text{max}} (mg/L) 7.39 (4.98–9.80) | 7.39 (4.98–9.80) | NS (0.413) |
|            | C_{\text{min}} (\mu g/mL) 3.19 | 3.19 (2.18–4.19) | NS (0.909) |
|            | AUC_{0–4h} (l/h/mL) 8.50 | 8.50 (6.69–10.32) | NS (0.774) |

Continued
| Reference                          | Study design                          | No. of subjects (co-infected; on ART at enrolment) | Age of subjects (IQR/range/SD as reported) | PK drug; dose (IQR/range/SD as reported) | PK parameters | TB monoinfection (IQR/range/SD as reported) | HIV/TB co-infection (IQR/range/SD as reported) | Effect (P value) | Conclusion | Quality of evidence |
|-----------------------------------|---------------------------------------|---------------------------------------------------|------------------------------------------|---------------------------------------|---------------|---------------------------------------------|------------------------------------------------|----------------|-------------|---------------------|
| Yang, H. et al. (2018) 149        | NCA PK evaluating INH/RIF/PRZ/EMB PK in children with HIV versus without HIV | 100 (50; NR)                                       | 4.90% <5 years and 23.0% <2 years         | INH median (range) 11.4 mg/kg (9.7–12.9) | INH C<sub>max</sub> <3 mg/L (%) | 10.0%                                      | NS (1.000)                                         | HIV co-infection status was associated with low C<sub>max</sub> of RIF and EMB. | Very low   |                        |
| Bekker, A. et al. (2014) 143      | NCA PK evaluating INH PK in HIV-exposed versus unexposed newborns | 20 (16; 1) Median (IQR): 14 days (9–31)           | INH median (IQR) 10 mg/kg                | INH C<sub>max</sub> <8 mg/L (%) | 52.0%                       | 70.0% (OR 2.45; 95% CI 1.01–5.95) | NS (0.100)                                         | INH C<sub>max</sub> was found to be slightly lower in HIV-exposed infants. | Very low   |                        |
| McIlleron, H. et al. (2009) 17    | NCA PK evaluating INH PK in children with HIV versus without HIV | 56 (22; NR) Median (IQR): 3.22 years (1.58–5.38) | INH median (IQR) 5.01 mg/kg (4.35–9.24)  | INH C<sub>max</sub> <2 mg/L (%) | 46.9%                       | 77.1% (OR 5.37; 95% CI 1.87–15.37) | NS (0.003)                                         | HIV infection was not associated with differences in INH C<sub>max</sub>. | Low        |                        |
| Second-line TB treatment         |                                       | 109 (16; 13 LPV/r, 3 EFV) Median (range): 2.1 years (0.3–8.7) | LVX q24h 15 or 20 mg/kg                  | LVX C<sub>max</sub> (mg/L) NR | 4.70 (4.37, 5.00) | NR                                           | 15.9% (26.6 to 59.3) | HIV infection was associated with a lower LVX clearance, although unlikely to be clinically significant. | Very low   |                        |
| Garcia-Prats, A. J. et al. (2015) 154 | NCA PK evaluating OFX PK in children with HIV versus without HIV having MDR-TB | 85 (11; NR) Median (IQR): 3.4 years (1.9–5.2) | OFX q24h 20 mg/kg                        | OFX C<sub>max</sub> (mg/L) | 4.44 (10.6) | 42.5 (9.0) | NS (0.560) | No effect of HIV infection on OFX PK was observed. | Low        |                        |
| Garcia-Prats, A. J. et al. (2019) 159 | NCA PK evaluating LZD PK in children with HIV versus without HIV having MDR-TB | 48 (3; NR) Median (range): 4.6 (0.6–15.3) years | LZD q2h 10 mg/kg (<10 year) LZD q2h 10 mg/kg (<10 year) | LZD C<sub>max</sub> (mg/L) | 9.05 (2.44) | 8.42 (1.51) | NS (0.040) | Study was underpowered to show a clinically relevant effect of HIV on LZD PK. | Very low   |                        |
| Study | Design | Population | Median (range) | Drug | Dose | Bioavailability Reduction (%) | Concentration | Comments |
|-------|--------|------------|----------------|------|------|---------------------------|--------------|----------|
| Bjugard Nyberg, H. et al. (2018) | PopPK evaluating ETH PK in children with HIV versus without HIV having MDR-TB | 119 (24; 14 LPV/r, 6 EFV) | 2.6 years (0.25–15) | ETH | q24h 20 mg/kg | Difference in bioavailability (%) | – | Very low |
| Liwa, A.C. et al. (2013) | NCA PK evaluating PAS PK in children with HIV versus without HIV having MDR-TB | 10 (4; 4 EFV) | Median: 4 years (1–12) | PAS | q12h 75 mg/kg or q24h 150 mg/kg | AUC0–24h (µg h/mL) | NR | Very low |
| Thee, S. et al. (2014) | NCA PK evaluating OFX and LVX PK children with HIV versus without HIV having MDR-TB | 22 (4; NR) | Median (IQR): 3.14 years (1.3–4.0) | OFX | q24h 20 mg/kg | Median (IQR) Cmax (mg/L) | 6.88 (5.36–8.06) | Very low |
| Thee, S. et al. (2015) | NCA PK evaluating MXF PK in children with HIV versus without HIV having MDR-TB | 23 (6; 2 LPV/r, 4 EFV) | Median (IQR): 11.1 (9.2–12.0) | MXF | q24h 10 mg/kg | Median (IQR) AUC0–24h (µg h/mL) | 19.98 (16.71–25.21) | Very low |
| Thee, S. et al. (2011) | NCA PK evaluating ETH PK in children with HIV versus without HIV having MDR-TB | 31 (7; 7) | Range: 3 months–13 years | ETH | q24h 15–20 mg/kg | AUC0–24h (µg h/mL) | NR | Very low |

AMK, amikacin; ATT, antituberculosis treatment; q12h, twice daily; EMB, ethambutol; ETH, ethionamide; EFV, efavirenz; FQ, fluoroquinolone; HIV, human immunodeficiency virus; INH, isoniazid; LVX, levofloxacin; LZD, linezolid; LPV, lopinavir; LPV/r, lopinavir/ritonavir; MFX, moxifloxacin; NCA, non-compartmental analysis; NR, not reported; OFX, ofloxacin; PAS, para-aminosalicylic acid; PK, pharmacokinetic; PK-PD, pharmacokinetics-pharmacodynamics; popPK, population pharmacokinetics; PZA, pyrazinamide; q24h, once daily; RIF, rifampicin; RIF-ATT, rifampicin-containing tuberculosis treatment; RTV, ritonavir; TIW, thrice weekly; TRD, terizidone.
compared with healthy adults. One study with healthy volunteers reported a 61% decrease in $C_{\text{trough}}$ due to rifampicin, and $C_{\text{trough}}$ remained 53% lower when double the dose of raltegravir (800 mg q12h) was given with rifampicin, compared with raltegravir (400 mg q12h) only. In contrast, a study in patients with HIV/TB co-infection suggested that doubling the dose of raltegravir overcompensates for rifampicin induction ($C_{\text{trough}}$ +68%), whereas the standard raltegravir dose with rifampicin resulted in only a 31% decrease in trough concentration of raltegravir. However, non-inferiority after 48 weeks of treatment could not be statistically demonstrated for raltegravir 400 mg q12h compared with efavirenz 600 mg q24h in adults with HIV-associated TB using rifampicin-based TB treatment simultaneously, and thus is not recommended as first-line therapy. PK parameters of adjusted doses of raltegravir have been studied in children 2–12 years old receiving 12 mg/kg q12h during concomitant rifampicin, instead of 6 mg/kg q12h.64 Geometric means of raltegravir AUC$_{0-12h}$ and $C_{\text{trough}}$ were within the predefined target range.65 In addition, raltegravir data in infants (4 weeks to 2 years old) have been published recently; doubling the dose of raltegravir chewable tablets (12 mg/kg; crushed and dispersed in water) while taking rifampicin achieved adequate PK levels and was found to be safe.66 Given the observed PK data in children with HIV/TB receiving double-dose raltegravir, this approach seems to be suitable for children receiving rifampicin concomitantly.

The use of bictegravir is not recommended in combination with rifampicin. Bictegravir exposure in healthy adults without HIV or TB was found to be 80% lower when dosed once daily with rifampicin, and doubling the dose by giving it twice daily did not mitigate the drug interaction, as exposures were still reduced by 60% in contrast to raltegravir and dolutegravir. This might be due to differences in metabolism; CYP3A4 and UGT1A1 equally contribute to bictegravir metabolism, whereas dolutegravir and raltegravir are mainly metabolized by UGT1A1.67 The clinical consequences of the bictegravir–rifampicin drug interaction have not been explored in patients. There have been no DDI studies in children receiving bictegravir together with TB drugs. Elvitegravir needs boosting by cobicistat to achieve therapeutic plasma concentrations and its metabolism is similar to that of bictegravir. There is no paediatric formulation of elvitegravir/cobicistat, hence it is only available for older children. Co-administration of elvitegravir/cobicistat and rifampicin has not yet been studied, but it is contraindicated because large decreases in elvitegravir/cobicistat exposure are expected.

There is no clinically meaningful effect of rifabutin on raltegravir and dolutegravir exposure in adults,68,69 but this has not yet been investigated in children. In adult patients with HIV, use of dolutegravir q24h together with rifapentine once weekly appeared to be well tolerated and led to a reduction of dolutegravir exposure that was probably not clinically significant.60 Raltegravir exposure was also found to be sufficient in healthy adults receiving concomitant rifapentine.61

Nucleoside reverse transcriptase inhibitors
Limited studies have been reported that assess NRTI PK in combination with rifampicin-based TB treatment in adults. Both abacavir and zidovudine are metabolized by UGT, and raltegravir is known to induce UGT.62 Two studies reported decreases of zidovudine exposure (close to −50%) due to concomitant use of rifampicin in HIV-infected adults.53,54 whereas no studies reported on abacavir PK in adults with TB treatment. Only one study reported on PK of NRTIs in children using rifampicin; the authors found an average decrease in abacavir exposure of 36% due to rifampicin-based TB treatment in children <6 years old also receiving super-boosted lopinavir/ritonavir.55 It is uncertain whether or not this is clinically relevant, since its antiviral effect is due to the intracellular anabolite, carbovir triphosphate, which was not measured56 and NRTI plasma concentrations do not necessarily correlate with antiviral activity of the drug.57 Also, ART always consists of multiple ARVs that might compensate for loss in efficacy of the other ARV. Of all children, 82% were virologically suppressed by the end of the study when receiving rifampicin-based TB treatment, which is in line with children without TB treatment.58

Tenofovir alafenamide is a substrate of drug transporters such as P-gp and breast cancer resistance protein.68 Rifampicin affects tenofovir alafenamide metabolism by inducing expression of these drug transporters.59 Plasma concentrations of tenofovir and tenofovir alafenamide and intracellular tenofovir diphosphate were reduced by concomitant use of rifampicin in adults. However, intracellular tenofovir diphosphate concentrations were still 4-fold higher compared with patients using tenofovir disoproxil, indicating that this might not be clinically relevant.60 No research has been done in children yet. Tenofovir disoproxil absorption is less P-gp dependent compared with tenofovir alafenamide. Therefore, tenofovir concentrations after tenofovir disoproxil treatment do not significantly change due to concomitant rifampicin either in healthy volunteers or in adults who are HIV/TB co-infected.61,62 Co-administered ritonavir-boosted ARVs can also potentially modify this interaction by ritonavir-related induction of P-gp and UGT.63 Super-boosted ritonavir seemed to contribute minimally to reducing abacavir exposure compared with rifampicin,64 but tenofovir alafenamide and tenofovir disoproxil PK has not yet been studied with co-administration of both rifampicin and ritonavir. Emtricitabine plasma concentrations and intracellular emtricitabine triphosphate concentrations were also found to be unaffected by rifampicin-based TB treatment in adults.65 Lamivudine PK has not been investigated at all in patients receiving rifampicin. Paediatric studies are needed to confirm the results of adult studies of NRTI PK and rifampicin, especially for tenofovir alafenamide and tenofovir disoproxil.

Non-nucleoside reverse transcriptase inhibitors
Metabolism of nevirapine is primarily through CYP3A4 and to a lesser extent CYP2B6, and therefore it is affected by rifampicin.66 Decreases of AUC$_{0-12h}$ (−58%) and $C_{\text{trough}}$ (−68%) have been reported in adults.67 In total, six studies reported on nevirapine PK parameters when co-administered with rifampicin in children. Two studies reported decreased nevirapine exposure (about 40%) due to rifampicin-based TB treatment given at 10 mg/kg68 and 15 mg/kg69 in children under 3 years old. Moreover, significantly more children on rifampicin compared with peers without rifampicin had nevirapine trough levels <3.0 mg/L (51% versus 0%67 and 61% versus 30%69), which is considered subtherapeutic. Both in newborns using rifampicin for TB prevention (10 mg/kg) and in children between 1 and 11 years old using rifampicin-based TB treatment, nevirapine trough concentrations were found to be reduced...
by about 30%.69,70 Shoh et al.71 found that increasing the nevirapine dose by 20%–30% in older children [mean (SD): 8.1 (3.3) years] receiving rifampicin-based TB treatment resulted in a similar exposure compared with children receiving nevirapine without rifampicin. Another study from Thailand, including eight children >3 years old with HIV-associated TB, found no children with inadequate nevirapine Ctrough during rifampicin co-administration.72 This might be due to genetic differences in Thai children or the low number of children included in the study. Overall, most studies report reduction of nevirapine exposure in children receiving rifampicin-based TB treatment. The WHO recommends the use of nevirapine at the maximum weight/age-appropriate dose (200 mg/m2) only in children with HIV/TB under 3 years old, but not for older children because of other available options with more robust ARVs.73

Efavirenz is metabolized to an inactive metabolite mainly by CYP2B6 and to a lesser extent by CYP2A6 and UGT2B7.74 The prevalence of CYP2B6 polymorphisms is high in TB- and HIV-endemic areas such as Asia and sub-Saharan Africa (range: 10%–28% slow metabolizers and 34%–50% extensive metabolizers), resulting in wide efavirenz PK variability.75,76 Rifampicin is known to induce CYP2B6,77 leading to a decrease of efavirenz AUC by 26% when used with efavirenz in healthy adults.76 In contrast, isoniazid might contribute to an increase in efavirenz exposure by inhibiting CYP2A6 activity.77 No clinically significant alterations in efavirenz PK were found in adults with HIV-associated TB using efavirenz 600 mg q24h and rifampicin/isoniazid-based TB treatment; genetic CYP2B6 polymorphisms had a larger impact on efavirenz exposure.75 Recent PK data suggest that efavirenz 400 mg q24h can also be considered in adults and adolescents.76 The efavirenz PK profile is favourable when administered with rifapentine and isoniazid in adults, but has not been investigated in children.79 The potential interaction between efavirenz- and rifampicin-based TB treatment in children was investigated in seven studies. No substantial differences in efavirenz PK were seen in children >3 years old using low-dose first-line TB treatment.71,80–82 More recently, a PK study including 144 children between 3 and 14 years old confirmed these findings with higher isoniazid (10 mg/kg) and rifampicin (15 mg/kg) dosages being given.83 Efavirenz PK parameters were slightly higher in patients on rifapentine/isoniazid-based TB treatment, but these findings were not considered to be clinically relevant.83

McIlerson et al.84 showed that average efavirenz mid-dose interval concentrations increased by 1.49-fold in children with CYP2B6 slow metabolizer genotypes when receiving concomitant rifampicin/isoniazid-based TB treatment compared with efavirenz without TB drugs. No differences were found in children with genotypes for intermediate and fast CYP2B6 metabolism.85 This finding is explained by the assumption that the inhibitory effect of isoniazid on CYP2A6 becomes more relevant in slow CYP2B6 metabolizers.85 Another study assessed efavirenz PK in HIV/TB-co-infected children <3 years old with a genotype-based dosing approach.86 Poor metabolizers were given 25% of the efavirenz dose, and the efavirenz dose was increased by ~30% for all children who received rifampicin-based TB treatment, regardless of CYP2B6 genotype. Increasing the dose was not necessary, since 66% of all included children had supratherapeutic Ctrough (>4.0 mg/L). PK variability was high in this study despite genotype-based dosing.86 Due to highly variable efavirenz PK, efavirenz is not generally recommended in children aged <3 years.73 Although efavirenz exposure is largely dependent on CYP2B6 and CYP2A6 genotype, genotype testing is expensive and genotype-based efavirenz dosing is not practical, and therefore it is not recommended.73 No efavirenz dose adjustments are necessary for children and adults during rifampicin-based TB treatment.

Use of doravirine, etravirine or rilpivirine together with rifampicin-based TB treatment is contraindicated. All these NNRTIs are mainly metabolized through CYP3A4.87 Enzyme induction by rifampicin leads to large decreases in doravirine, etravirine and rilpivirine exposure in adults; AUC0–tau –88%, AUC0–12h about –55%, and AUC0–24h –80%, respectively.90 No studies have been done in children.

Protease inhibitors

PK parameters are an important indicator for lopinavir efficacy. Mohalisa et al.91 found that virological failure correlates with lopinavir trough concentrations below 1.0 mg/L. Lopinavir is co-administered with ritonavir, a potent inhibitor of CYP3A, in a 4:1 ratio to achieve higher (effective) lopinavir exposure. Rifampicin is a strong inducer of CYP3A,32 leading to large decreases in plasma concentrations of lopinavir (AUC –75%) in healthy adults.92 The interaction can be overcome by doubling the lopinavir/ritonavir dose92,93 but, due to an increased risk of hepatotoxicity, this is not recommended.94 Replacement of rifampicin by rifabutin (150 mg q24h) due to bidirectional DDI is preferred for first-line TB treatment in adults, because rifabutin has little effect on lopinavir/ritonavir exposure.76 Lopinavir/ritonavir currently is the preferred anchor drug in ART for children younger than 3 years old.73 Bioavailability of lopinavir is reduced by 25% in adults due to co-administration of rifampicin-based TB treatment, whereas bioavailability decreases by 59% in children.95 To compensate for this DDI, three strategies have been studied in children; double-dose lopinavir/ritonavir (ratio 8:2), 8 hourly lopinavir/ritonavir dosing (ratio 4:1) and super-boosting by increasing the ritonavir dose to 1:1 ratio with lopinavir.

A PK proof-of-concept study found that the lopinavir/ritonavir super-boosting strategy (ratio 1:1) was effective in attenuating enzyme induction by rifampicin in children.96 Although lopinavir AUC was 31% lower96 and clearance 30% higher97 in children while on rifampicin-based TB treatment compared with off TB treatment, lopinavir Ctrough was similar and 13/15 patients had therapeutic trough levels (>1.0 mg/L). The efficacy of this strategy was later confirmed in a larger modelling study in children of 3–15 kg (including infants <1 year) by showing non-inferiority of lopinavir Ctrough during rifampicin co-treatment.98 The researchers predicted that 92% of all patients receiving super-boosted lopinavir/ritonavir with rifampicin would reach trough concentrations above 1.0 mg/L. Overall, super-boosted lopinavir/ritonavir was well tolerated, even though caregivers reported difficulties administering extra ritonavir because of low acceptability of the drug formulation.99 Super-boosted lopinavir/ritonavir also resulted in similar lopinavir exposure in malnourished children with HIV/TB co-infection compared with children without TB treatment.99

Double-dosed lopinavir/ritonavir (ratio 8:2) in children younger than 3 years old (n = 17; median age 1.25 years) receiving rifampicin-based TB treatment resulted in inadequate lopinavir trough concentrations compared with children receiving...
lopinavir/ritonavir without TB treatment. Only 40% of children receiving lopinavir/ritonavir double dose had C_{trough} greater than 1.0 mg/L, whereas 92% of the control group achieved therapeutic trough concentrations. The differences between children and adults were explained by a lower bioavailability of lopinavir due to low ritonavir concentrations. Double-dosed lopinavir/ritonavir given with rifampicin has not been studied in children >3 years old.

Based on simulations from a population PK model, it was expected that at least 95% of children would have lopinavir trough concentrations of at least 1.0 mg/L when using lopinavir/ritonavir thrice daily in combination with rifampicin-containing TB treatment. However, a study in children with HIV-associated TB reported that 36% of 11 children did not achieve lopinavir C_{trough} >1.0 mg/L when using this treatment strategy.

The effect of MDR-TB drugs on lopinavir/ritonavir PK was assessed in one small study which included 16 children receiving combinations of high-dose isoniazid, pyrazinamide, ethambutol, ethionamide, terizidone, a fluoroquinolone and amikacin, and 16 controls without MDR-TB. No significant differences were found between the two groups; 81% of children with MDR-TB versus 88% of controls had therapeutic C_{trough}.

Atazanavir, darunavir and saquinavir are contraindicated in adults when co-administered with rifampicin due to safety and efficacy concerns. Ritonavir-boosted atazanavir co-administered with rifampicin resulted in very large decreases in exposure of atazanavir (AUC_{tau} – 72%; C_{trough} – 98%). For darunavir, doubling the dose when used twice daily resulted in similar C_{trough} compared with normal doses without rifampicin in adults with HIV. However, this study was discontinued early due to severe hepatotoxicity, as were studies with co-administration of rifampicin and ritonavir-boosted atazanavir or saquinavir. No studies have been conducted with boosted PIs other than lopinavir/ritonavir in HIV/TB co-infected children. The effect of ritonavir-based TB treatment on cobicistat-boosted PIs has not been determined yet. Concomitant use of rifabutin slightly increased darunavir exposure and had very little effect on atazanavir PK in healthy volunteers. Co-administration of rifapentine and PIs has not been studied, but is expected to result in large decreases of PI plasma concentrations.

**Effects of ART on TB drugs**

**First-line TB drugs**

Metabolism of rifampicin and rifapentine is through esterases in liver microsomes and to some extent by renal excretion. The major metabolism pathways of isoniazid are by acetylation through N-acetyltransferase 2 (NAT2) and hydrolysis through amidase. Pyrazinamide is converted into pyrazinoic acid by microsomal deamidase and further metabolized by xanthine oxidase enzymes. Approximately 80% of ethambutol is excreted renally and 20% is metabolized by alcohol dehydrogenase. None of these metabolic pathways is expected to be affected by ARVs.

Rifabutin is both an inducer and a substrate of CYP3A, so DDIs with ARVs are potentially bidirectional. It is predominantly metabolized into its equally active metabolite 25-O-desacetylrifabutin by CYP3A4. This metabolite accounts for up to 10% of the total antimicrobial activity of rifabutin in adults without interacting medication. Efavirenz is known to decrease rifabutin plasma concentrations through induction of CYP3A4, but this interaction has not been studied in children.

Lopinavir/ritonavir is known to interact with rifabutin through inhibition of CYP3A enzymes by ritonavir, leading to high exposure of rifabutin and its active metabolite, and an increased risk of dose-dependent toxicities such as uveitis and bone marrow depression. Recently, the dose recommendation of rifabutin was increased from 150 mg thrice weekly to 150 mg q24h when co-administered with lopinavir/ritonavir instead of 300 mg q24h without interacting medications. This DDI was studied in children under 5 years old that were already cured of TB receiving 5 mg/kg rifabutin thrice weekly instead of the recommended 10–20 mg/kg q24h without lopinavir/ritonavir. The study was discontinued because the neutrophil count declined in all six children receiving both rifabutin and lopinavir/ritonavir, two of them experienced grade 4 neutropenia. Surprisingly, rifabutin C_{max} was below the target range for therapeutic drug monitoring (0.45–0.9 mg/L) in four out of six children. The median rifabutin and 25-O-desacytlrifabutin exposures were higher compared with most studies in adults using thrice-weekly 150 mg rifabutin co-administered with lopinavir/ritonavir, but lower compared with adults receiving 150 mg rifabutin q24h with lopinavir/ritonavir. Rawizza et al. rarely found neutropenia in 48 young children with HIV-associated TB [median (IQR) age: 1.7 years (0.9–5.0)] receiving a 6 month course of 2.5 mg/kg/day rifabutin and lopinavir/ritonavir, although the absolute neutrophil count declined slightly. The rifabutin course was completed with no TB symptoms in 97% of participants after 12 months of follow-up. The different safety findings were suggested to be caused by differences in patient characteristics, i.e. children who were HIV infected versus HIV/TB co-infected. Rifabutin-associated neutropenia has also been observed more frequently in healthy adults compared with adults with HIV-associated TB. Rawizza et al. also presented an interim analysis of eight older children [median (IQR) age: 13.5 years (12.8–14.3)] receiving 2.5 mg/kg/day rifabutin with lopinavir/ritonavir. Rifabutin and 25-O-desacyltrifabutin exposure in these children was slightly lower compared with the findings of Moultrie et al. (see Table 1), whereas C_{max} of both substances was comparable. Exposure of 25-O-desacyl rifabutin was 4-fold higher compared with adults receiving rifabutin 300 mg q24h without lopinavir/ritonavir, which is consistent with data from Moultrie et al. and adults receiving rifabutin with lopinavir/ritonavir, and is not expected to be harmful. These preliminary PK results suggest that rifabutin can be used safely in children >5 years old using rifabutin at 2.5 mg/kg/day with lopinavir/ritonavir, but regular laboratory and clinical monitoring is essential. Younger children are to be investigated in this study to confirm this dosing strategy among all children.

**Second-line TB drugs**

In children, no research has been conducted to investigate the effect of ART on exposure of medications used for MDR-TB. Potential interaction mechanisms and data from adult studies are described below and grouped by class defined by the WHO MDR-TB treatment guideline.
This potential DDI requires further investigation to determine its mechanism and clinical relevance.

Delamanid is metabolized by albumin into its primary metabolite (DM-6705). Subsequently, CYP3A4 is the main metabolic pathway for DM-6705. Co-administration of tenofovir disoproxil and efavirenz did not change delamanid exposure in healthy adults, and giving lopinavir/ritonavir resulted in a 25% increase of delamanid. Further investigation is required.

**Effects of HIV infection on PK of TB drugs**

### First-line TB drugs

The effect of HIV infection on the PK of TB drugs in children has been examined in multiple studies, but most were inconclusive. It is believed that malabsorption or malnutrition due to HIV infection might cause low exposure to TB treatment in HIV patients. Strict mg/kg dosing also contributes greatly to these inconclusive results, since it assumes a linear relationship between body weight and clearance despite the fact that the relationship is more likely to be allometric; not taking a patient’s age into account can result in severe under-dosing, especially in underweight children. None of the included studies reported on the impact of ART use or certain antiretroviral agents, because of small sample sizes, heterogeneity in ART or absence of ART, and lack of mechanistic explanations for potential interactions. Hence, it is uncertain whether the observed results are because of HIV infection, ART or differences in the populations. A systematic review was published about the influence of HIV infection on the PK of TB treatment. It mainly focused on adults without reporting a comprehensive analysis in children. The authors were unable to generate recommendations with respect to dosing of TB treatment in patients with HIV-associated TB due to heterogeneity and inconsistency of data.

Results of all studies in children are summarized in Table 2. Apart from two studies reporting a slight decrease of isoniazid, most did not find lower isoniazid exposure in children with HIV infection compared with TBmono-infected children. The overall effect of HIV infection on isoniazid PK seems not to be clinically relevant in children.

Various studies reported lower rifampicin Cmax (range: −17% to −49%) and AUC (range: −24% to −56%) values in children who are HIV/TB co-infected (children both on and off ART) compared with TBmono-infected children. Rifampicin clearance increased and bioavailability decreased in children with HIV. This effect was associated with HIV/TB co-infection rather than the use of ART. Other studies did not find statistical differences, probably because of small sample size and limited power. The large decreases in rifampicin exposure can be clinically relevant.

PK data of pyrazinamide in children with HIV and TB compared with HIV-uninfected children was heterogeneous. Some showed a slight decrease in AUC or Cmax in co-infected children, but most reported varying non-significant results. The impact of HIV infection on pyrazinamide PK in children seems relatively small and variable.

Almost all studies investigating ethambutol PK reported lower ethambutol AUC (range: −40% to −60%) and lower ethambutol Cmax (range: −40% to −70%) in children that were HIV-infected.
compared with uninfected children. One small study (n = 18) found low ethambutol Cmax values regardless of HIV status. Nevertheless, ethambutol exposures generally are substantially lower in HIV-infected children compared with uninfected children. It is unclear whether usage of ART affected PK of ethambutol.

In most studies, children with HIV/TB co-infection had significantly lower weight for age Z-scores due to disease severity or malnutrition. These differences aggravate the assessment of the relationship of lower exposure with HIV/TB co-infection, since lower exposure can partly be explained by relatively higher clearance/kg because of low weight and high fat-free mass. Dosing of TB drugs based on lean body weight might take these issues into account and lead to better exposure in children who are underweight.

**Second-line TB drugs**

The effect of HIV infection and ART on PK of drugs used for MDR-TB has been investigated in a few studies in children. Only second-line TB drugs that have been studied in children are described here, split by MDR-TB treatment class.

**Group A.** Exposure of moxifloxacin was found to be significantly lower (AUC0–24h– 34%) in children living with HIV using ART [lopinavir/ritonavir- (2/6) or efavirenz-based (4/6) regimen] compared with 17 HIV-uninfected children. For levofloxacin and ofloxacin, no significant differences in PK parameters were seen in children with HIV/TB co-infection (both on and off ARVs) compared with children without HIV, which is consistent with findings in adults. A population PK study reported a 15.9% reduction in levofloxacin clearance in 16 children with HIV between 0.3 and 8.7 years old receiving ART (lopinavir/ritonavir- or efavirenz-based regimen), but this was not considered clinically relevant. One study assessed linezolid PK in children with HIV, but could not detect any effect of HIV infection owing to the small dataset (n = 3).

**Group B.** No PK studies have been done for clofazimine and terizidone/cycloserine in children with HIV.

**Group C.** A non-significant trend towards lower p-aminosalicylic acid exposure was reported in children who were HIV infected (n = 4; all on efavirenz). Ethionamide concentrations were found to be significantly lower in children with HIV (n = 7) at both 1 and 4 months after initiation of therapy compared with uninfected peers. Bjugard Nyberg et al. suggested that ethionamide concentrations were lower because of decreased bioavailability (~21%) in HIV-infected children, of whom most were on ART (efavirenz or lopinavir-based regimen). No significant differences were seen between children receiving lopinavir/ritonavir-based ART, efavirenz-based ART or no ART.

**Discussion**

To our knowledge, this is the first review on the PK of (MDR-)TB drugs and ART in children with HIV-associated TB using a comprehensive systematic and scoping approach. Information from adult studies was also included to identify knowledge gaps and differences between DDIs in children versus adults. This systematic review shows that the number of treatment options is increasing for children with HIV/TB co-infection, but there are still many knowledge gaps when it comes to DDIs between TB drugs and ART. We identified 47 eligible studies; most of them focused on lopinavir/ritonavir, efavirenz, nevirapine and first-line TB treatment.

PK differences between adults and children are common. Differences in membrane permeability, gastric pH and emptying time, plasma protein binding, total body water and fat, organ size, maturation and abundance of metabolizing enzymes and drug transporters, and development of renal function can cause differences in absorption, distribution, metabolism and excretion (ADME) of medications, which changes with age and can affect the severity of DDIs. The paediatric population itself also consists of multiple subpopulations that have different PK profiles. The FDA distinguishes newborn infants (0–28 days), infants and toddlers (28 days to 2 years), children (2–12 years) and adolescents (12–16 or 18 years). Younger children mainly differ from adults due to immaturity of hepatic enzymes, whereas older children often have increased drug clearance. This can result in different recommendations for DDI management. For example, the interaction between rifampicin and lopinavir/ritonavir was found to be different in young children (<3 years old) from that in adults; double-dosing of lopinavir/ritonavir resulted in adequate lopinavir concentrations in adults, but led to subtherapeutic concentrations in children. There were no data to confirm these differences in older children. Another example is the interaction between rifampicin and raltegravir. Doubling the dose of raltegravir q12h was needed to overcome the interaction with rifampicin in children, whereas exposure in adults seemed therapeutic when normally dosed raltegravir q12h. These examples illustrate that DDIs and strategies to overcome DDIs should preferably be tested in children from all different paediatric subpopulations before adult recommendations can be extrapolated. Different formulations given to children can also influence PK of drugs; for example, sorbitol (as excipient) affects absorption of lamivudine.

In addition, data on pharmacodynamic differences in the paediatric population compared with adults and their impact on DDI management are scarce, and this requires further investigation.

Extrapolation of adult PK data by means of population PK modelling offers a great opportunity to identify new treatment strategies to avoid toxicity or suboptimal therapy due to DDIs in children. However, conducting confirmatory PK studies remains essential in assessing the magnitude of DDIs in children. Extrapolating double-dosed lopinavir/ritonavir with concomitant rifampicin-based TB treatment from adults on solid formulation to young children on liquid formulation could not be confirmed in clinical studies. Physiologically based PK models can help to better characterize these complicated interactions and improve predictions of dosing regimens appropriate to overcome DDIs in children.

Current treatment guidelines recommend using super-boosted lopinavir/ritonavir-based ART during rifampicin-based TB treatment for children <3 years old. Nonetheless, double-dosed lopinavir/ritonavir is still given frequently in resource-limited settings to children who are HIV/TB co-infected. Super-boosted lopinavir/ritonavir is hard to prescribe and administer, because the separate ritonavir oral solution has a bitter taste, a short shelf-life, requires refrigeration and stock-outs occur regularly. A new lopinavir/ritonavir super-boosted formulation is needed to ensure proper
therapy for children with HIV and TB who need to be treated with this drug combination. This interaction can be bypassed by using rifabutin instead of rifampicin. However, lopinavir/ritonavir increases rifabutin exposure, the dose in young children with HIV has not yet been established and global access to rifabutin is limited. Efavirenz is registered for children aged 3 months and older weighing more than 3.5 kg, but only recommended for use in children >3 years old, because of high PK variability. Slow CYP2B6 or CYP2A6 metabolizers are at high risk of having high efavirenz exposure and toxicity. Polymorphisms resulting in slow CYP2B6 or CYP2A6 metabolism commonly occur, regardless of ethnic group. Efavirenz plasma concentrations are even more increased in slow CYP2B6-metabolizing children receiving rifampicin/isoniazid-based TB treatment due to the inhibitory effect of isoniazid on CYP2A6, whereas efavirenz PK did not alter in fast and intermediate metabolizers. Slow CYP2B6-metabolizing children receiving efavirenz and rifampicin/isoniazid-based TB treatment thus are at an extra high risk of having toxic efavirenz plasma concentrations. It is therefore of utmost importance to be cautious when administering efavirenz to children with TB who are under 3 years of age. A triple NRTI regimen is also advised by the WHO guidelines for children with HIV/TB co-infection using rifampicin-based TB treatment. This recommendation is based on a large trial done in HIV-infected children who were switched to triple NRTIs after a treatment initiation phase with NNRTI-based ART. These children, however, did not receive rifampicin-based treatment, which may reduce exposures to key NRTIs such as zidovudine and abacavir. This study reported similar short-term maintenance of viral suppression for a triple NRTI (including abacavir) regimen compared with an NNRTI-based regimen, but the triple NRTI regimen was inferior at 12 months. Using a triple NRTI regimen has also been shown to be inferior to ART that contains an NNRTI-based TB treatment. Moreover, NRTI levels in children using TB treatment has only been investigated in one study, which found reduced abacavir levels. Hence, using a triple NRTI regimen should be considered as a last resort option in the treatment of paediatric HIV/TB co-infection when no other options are available. Seemingly fewer issues are expected with interactions between INSTIs and rifampicin-based TB treatment, since the paediatric formulations will be taste-masked and available in solid formulations, they are relatively safe, can easily mitigate rifampicin induction by giving it q12h (dolutegravir) or double dosed (raltegravir) and exhibit a predictable PK profile (dolutegravir). Therefore, worldwide access to paediatric INSTIs should be prioritized to improve ART in children with HIV-associated TB.

In general, target exposures of TB treatment are often not met in HIV-uninfected children. Higher TB treatment dosing schedules should be considered and are currently being investigated in children with and without HIV. Data about the effect of HIV infection on PK of first-line TB drugs in adults and children are still inconclusive. In children who are HIV co-infected, significant decreases in exposure of rifampicin and ethambutol were seen, regardless of ART use. However, these studies were very heterogenous and usually not powered to assess this comparison. These reduced serum levels might be attributed to malabsorption caused by malnutrition, diarrhoea, DDIs or concurrent gastrointestinal infections. The WHO guideline for treatment of paediatric TB does not distinguish between children with or without HIV regarding the required dose of first-line TB drugs. A more thorough investigation of the association of HIV with low TB drug exposures is warranted to tease out the impact of lower weight for age Z-scores and explore strategies to optimize dosing for treatment of TB as well as LTBI and MDR-TB (e.g. based on ideal body weight).

Little is known about DDIs of drugs for treating MDR-TB and ARVs in children. Most studies included in this review were not powered to assess PK differences between HIV-infected and uninfected children with or without ART. Studies in adults have shown that there are DDIs between ARVs and MDR-TB drugs that might be clinically relevant. No relevant paediatric PK data on new MDR-TB drugs (bedaquiline and delamanid) for HIV/TB co-infection are expected in the upcoming years. However, IMPACT has started studies with these drugs, including children with and without HIV. A table of ongoing research is included in the Supplementary data.

The overall quality of evidence of paediatric studies assessing PK of ART and TB treatment in HIV/TB co-infected children was low for many medications. In clinical practice, therapeutic drug monitoring (TDM) helps clinicians to make informed dosing decisions in case of DDIs. TDM offers a good opportunity for real-life monitoring of the magnitude of a DDI in an individual. However, this option is not widely available in countries that have a high burden of paediatric HIV and TB. There are still many knowledge gaps in PK research in children who are HIV/TB co-infected. The main gaps that warrant further research are listed in Table 3.

Some new medications, drug formulations and treatment strategies for the treatment of HIV and TB that are currently only used for adults are promising for future paediatric HIV/TB care. These drugs and treatment strategies come with some implications regarding DDIs in children. For HIV treatment, a long-acting injectable intramuscular formulation of cabotegravir (INSTI) and rilpivirine (NNRTI) is expected to be marketed in the near future. The use of cabotegravir/rilpivirine is currently also being investigated in children and adolescents in the MOCHA trial. However, no clinical studies have yet been done to assess the interaction of TB treatment with long-acting cabotegravir/rilpivirine. Rifampicin decreases orally administered cabotegravir AUC0–inf by 59% and rilpivirine AUC0–24h by 80% in adults. A physiologically based PK modelling study suggests that cabotegravir AUC0–28d and C_{ trough} will decrease by 41% and 46%, respectively, while rilpivirine AUC and C_{ trough} will both decrease by 82% when given with rifampicin.

With regards to TB treatment, there is increasing interest in the use of high-dose rifampicin to shorten the duration of TB treatment. Since rifampicin follows non-linear PK, a higher dose generally results in a disproportionate increase of rifampicin exposure. Little is known about the impact of high-dose rifampicin on its induction potential and PK parameters of ARVs. This is especially interesting for children in the lowest weight bands who often have very low rifampicin exposure following current paediatric dose recommendations. A recent study showed that efavirenz concentrations remained therapeutic in adult patients receiving double-dosed rifampicin as part of their TB treatment, despite a slight trend towards lower efavirenz concentrations. However, these findings cannot be extrapolated to children or other ARVs due to differences in enzyme activity and different metabolic
A 12 week treatment course with rifapentine and isoniazid once weekly is now recommended for children >2 years old and is recommended for all children >2 years old with HIV living in areas with high TB prevalence. However, little is known about the interaction potential of rifapentine in children. Recently, a new drug for MDR-TB has been approved by the FDA—pretomanid. About 20% of it is metabolism is through CYP3A, resulting in significant decreases in PK due to concomitant efavirenz in healthy volunteers, but not when used with lopinavir/ritonavir.186 Paediatric pretomanid trials are being planned by IMPAACT and TB alliance together.

Our review has limitations. First, many PK studies are included in this review that have small sample sizes and/or are underpowered. We took this into account for the final conclusions by scoring the quality of evidence for all studies. Second, this study focuses mainly on PK of the specific drugs, but not necessarily on efficacy and overlapping toxicity because these are usually not investigated in children with HIV/TB co-infection.

In conclusion, our review provides a comprehensive overview of all PK research done to assess DDIs between ARVs and TB treatment in HIV/TB-co-infected children. Only a few HIV treatment options are currently available and acceptable in children in the youngest age groups receiving rifampicin-based TB treatment; new treatment strategies are urgently needed. Future research should focus on evaluating dosing regimens for integrase inhibitors in all age groups and assessment of DDIs between ART and second-line TB drugs. Other dosing strategies of TB treatment should be considered for HIV-infected children because of low drug exposures and survival in this population.

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