A quest to optimize the clinical pharmacology of tuberculosis and human immunodeficiency virus drug treatment

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A systematic review on the effect of HIV infection on the pharmacokinetics of first-line tuberculosis drugs

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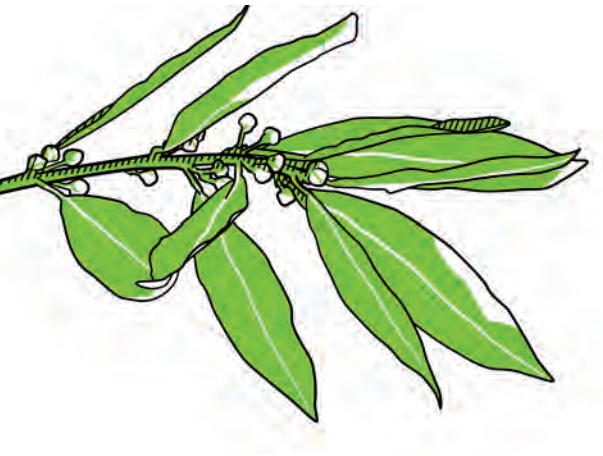

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Abstract

Objectives

Contrasting findings have been published regarding the effect of human immunodeficiency virus (HIV) on tuberculosis drug pharmacokinetics. The aim of this systematic review is to investigate the effect of HIV-infection on the pharmacokinetics of the first-line tuberculosis drugs (FLD); rifampicin, isoniazid, pyrazinamide and ethambutol by assessing all published literature.

Methods

Searches were performed in Medline through PubMed and EMBASE to find original studies evaluating the effect of HIV-infection on the pharmacokinetics of FLD. The included studies were assessed for bias and clinical relevance. Pharmacokinetic data were extracted to provide insight in the difference of FLD pharmacokinetics between HIV-positive- and HIV-negative tuberculosis patients. This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement and its protocol was registered at PROSPERO with registration number CRD42017067250.

Results

Twenty-seven studies were eligible for inclusion. The available studies provide a heterogeneous dataset from which consistent results could not be obtained. In both HIV-positive and HIV-negative tuberculosis groups rifampicin (13 out of 15) and ethambutol (4 out of 8) peak concentration (C_{max}) often did not achieve the minimum reference values. More than half of the studies (11 out of 20) which included both HIV-positive and HIV-negative TB groups showed statistically significant altered FLD AUC and/or C_{max} for at least one FLD.

Conclusion

HIV infection may be one of several factors that reduce FLD exposure. We could not make general recommendations with respect to the role of dosing. There is a need for consistent and homogeneous studies.

Introduction

Tuberculosis (TB) is an infectious disease caused by the organism *Mycobacterium tuberculosis.* Despite concerted efforts TB has remained a major global health problem [1]. With an estimated total of 1.8 million TB deaths in 2015 including 0.4 million TB related deaths among human immunodeficiency virus (HIV) infected persons, TB is a leading infectious killer worldwide [1]. Although improvements have been made in the prevention and treatment of HIV, 2.1 million new HIV infections worldwide were reported in 2015, resulting in a total of 36.7 million people living with HIV globally [2]. The risk of developing TB is 17 – 22-fold higher for people living with HIV, making HIV the most important predisposing factor for TB [3,4]. TB and HIV are known to act synergistically on the decline of the host immune response, which is fatal if left untreated [5,6].

The treatment of drug susceptible TB consists of four first-line TB drugs (FLD): isoniazid (INH), rifampicin (RIF), pyrazinamide (PZA) and ethambutol (EMB) [7]. Due to the limited resources in regions with a high TB burden, the World Health Organisation (WHO) advocates standardized treatment with generic, fixed-dose combination formulation tablets (FDC) for reasons of adherence, costs and logistics [7]. The recommended regimen consists of a two-months intensive phase with all four FLDs and a four-months continuation phase with RIF and INH only [7]. Despite the utilization of weight banded dosing high pharmacokinetic (PK) variability has been reported for the FLDs in studies investigating the PK of FLDs [8-10]. The hollow-fiber infection model and murine model conducted with the four FLDs showed that their effectiveness is best reflected by the area under the concentration-time curve (AUC) to minimum inhibitory concentration (MIC) ratio [9,11-13]. Notably, high PK variability and inadequate TB drug exposure are undesirable as high drug concentrations could lead to toxicity, while low drug exposure predisposes to prolonged treatment, treatment failure, relapse and development of drug resistance [9,14-17]. Several factors are known to cause inter-individual PK variability, including body weight [18], sex [18,19], pharmacogenomics [20,21] and co-morbid conditions such as diabetes mellitus [19].

Contrasting findings have been published regarding the effect of HIV on TB drug PK variability. Some studies show reduced FLD exposure in HIV infected patients [22-24], while others found no impact of HIV co-infection [25,26]. TB drug concentrations are an important determinant of clinical response to treatment [27] and any potential negative effect of HIV co-infection on the PK of TB drugs is therefore crucial. Despite the WHO recommendation that all individuals living with HIV should be initiated on antiretroviral therapy (ART), resulting in high ART coverage of HIV-infected TB patients, the effect of HIV infection on the PK of FLDs remains relevant. The start of ART does not improve the clinical and immunological condition of the patient immediately and the high bacterial burden at the start of TB treatment increases the risk of acquired drug resistance if plasma drug concentrations are affected by HIV co-infection.

In high endemic TB areas, drug shortages delay ART initiation and HIV suppression is not always achieved with the available antiretroviral drugs. The aim of this systematic review was to investigate the impact of HIV infection on the PK of RIF, INH, PZA and EMB.

Methods

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [28]. The protocol was registered at PROSPERO with registration number CRD42017067250.

A specific clinical question was structured according to the population, intervention, comparison, outcome (PICO) approach. In this process, P represented HIV-positive patients with TB co-infection; I, treatment of drug-susceptible TB with rifampicin, isoniazid, pyrazinamide and ethambutol; C, HIV-negative TB patients and O, the drug concentration of rifampicin, isoniazid, pyrazinamide and ethambutol.

To retrieve relevant articles a systematic electronic database search was performed in Medline through PubMed and EMBASE on the 11th of June 2017 and an additional check for new published articles was conducted on the 29th of August 2018. The searches were assessed to find original studies evaluating the effect of HIV infection on the PK of RIF, INH, PZA and/or EMB. All published studies, without restriction on language and publication date, were eligible. Studies in adult and paediatric populations were included. In case healthy volunteers were included as a control group, the study was eligible for inclusion, provided that a group of HIV-infected patient without TB was included to assess the effect of HIV infection on the PK of the FLDs. Studies with HIV-positive patients on ART were also eligible for inclusion, provided that the effect of HIV infection on PK of the FLD was assessed and reported. Studies conducted in HIV-positive TB patients without a comparator HIV-negative TB group were included in the systematic review, but were not eligible for in-depth analysis. Reviews, letters, meeting and abstract posters and correspondence were excluded. Studies without PK data, drug-interaction studies and non-human studies were also excluded.

The used search terms were: (hiv[mesh] OR hiv infection[mesh] OR hiv[tiab] OR hiv infection[tiab]) AND (tuberculosis[mesh] OR tuberculosis[tiab] OR tb[tiab]) AND ((pharmacokinetics[mesh] AND antitubercular agents[mesh]) OR (pharmacokinetics[tiab] AND (antitubercular[tiab] OR “TB drugs”[tiab] OR antimycobacterial[tiab] OR “antituberculosis drugs”[tiab] OR isoniazid[tiab] OR rifampicin[tiab] OR rifampin[tiab] OR ethambutol[tiab] OR pyrazinamide[tiab])). The studies retrieved from both PubMed and EMBASE were pooled and duplicate articles were removed. First, we screened titles and abstracts for eligibility and full-text articles were read by the first author (A.D.) if abstract was

found to be eligible or in case of doubt. When the full-text article met all in- and exclusion criteria it was included in the systematic review. Primary references of the included studies were checked and included if relevant. A second reviewer (L.R.I.) conducted the article selection process independently and any discrepancies were resolved by discussion. In order to identify unpublished studies the website clinicaltrials.gov was searched.

One researcher (A.D.) first performed data extraction, using a pre-discussed structured form and the second researcher (L.R.I.) independently checked the data extraction afterwards. Variables included: age group (paediatric or adult), comparator group(s) and the HIV positive group were noted for the included articles. Dose, AUC, peak drug concentration (C_{max}) and half-life ($t_{1/2}$), time to reach peak drug concentration (T_{max}), distribution volume (V_d) and clearance (CL) were extracted from the included articles if available and stratified by group. The data were extracted and noted per drug of interest (RIF, INH, PZA and EMB). Corresponding authors were contacted by electronic mail for additional data request if relevant data were missing in the included studies. Finally, the possibility of pooling data from included studies was assessed based on the risk of bias assessment, PK calculation strategy and data presentation.

No validated tool for risk of bias assessment of pharmacokinetic studies was available. In the absence of such a tool, we assessed the risk of bias in a study by noting the presence or absence of essential components required for adequate interpretation of results of a PK study. This provided the opportunity to compare the included studies on risk of bias related to methods and design. The following components were checked: total sample size, inclusion of both HIV positive and HIV negative TB groups, proportion of participants with CD4+ <200 cells/μL or CD4%<12, proportion of HIV positive participants using ART, presence of an absorption test, report of PK altering morbidities (gastro-intestinal, hepatic or renal), assessment of interacting co-medication, calculation of the drug dosage per included group, report of directly observed therapy (DOT), number of plasma samples drawn per participant, description of specimen handling, usage of validated analytical methods, method of AUC calculation, AUC calculation, stratification of data by HIV infection and the number of participants that were lost to follow-up or died during the study period. Studies without a comparator group were only included in the narrative results and excluded from further analysis. The combination of the number of plasma samples and AUC calculation method (non-compartmental or model based) were used to determine whether a study had high or low risk of bias for AUC calculation. Five or more plasma samples per patient and utilization of a validated population pharmacokinetic model for all FLDs were considered low risk.

In addition to a narrative synthesis of the results, the main results per study and the effect of HIV infection on AUC and/or C_{max} and additional PK parameters - if available - were displayed in a table. The data from patients at different months of treatment or at different dosing

schemes were presented separately. When the AUC and/or C_{max} for both HIV-positive and HIV-negative TB groups were available, these results were plotted in histograms for each study, comparing the AUC and/or C_{max} between HIV groups. This provided the opportunity to demonstrate an overview of trends. The clinical relevance of our findings was assessed in accordance with European Medicines Agency (EMA) guidelines [29,30]. EMA guidelines including bio-equivalence cut-off values of <80% and >125% were also used to estimate the clinical relevance of the reported statistically significant differences. Studies showing a statistically significant difference in AUC with a HIV-positive/HIV-negative ratio of <80% or >125% were considered clinically relevant. Only studies reporting data stratified by HIV status were eligible for this analysis.

Results

In total 282 articles were retrieved from the searches in PubMed and EMBASE. Systematically assessing the retrieved articles resulted in 25 articles being eligible for inclusion. One additional article was a report of a preliminary analysis 31 of the study by Antwi et al. 32 and was therefore excluded. Two further articles were identified by reviewing the references of the first included articles 33,34, resulting in a total of 27 articles included in the current systematic review. No relevant unpublished studies were found in clinicaltrials.gov investigating the effect of HIV infection on the PK of the FLDs. A flowchart of the selection process is presented in figure 1.

All included articles were screened for the presence or absence of essential components as a means of bias risk assessment. Twenty studies were conducted with adults and 7 studies in children. Five studies only included an HIV-positive TB group while a comparator HIV-negative TB group was lacking [34-38], therefore these studies were excluded for further analysis. Thirteen studies only included HIV-positive TB participants not using ART [22-24,26,32,33,39-44], in 10 studies a proportion of HIV-positive participants was on ART [19,34,38,45-51] while 5 studies did not provide information on ART usage among HIV-positive TB patients [25,35-37,52]. In 11 studies a limited number of less than 5 blood samples was drawn for determination of drug concentrations [19,25,34,36,37,40,41,43,46,47,52]. Three studies included both an HIV-positive TB group and an HIV-negative TB group but did not provide the AUC and C_{max} stratified by HIV status [40,44,46]. Two studies only reported C_{max} [19,52]. One study determined the percentage of RIF excreted in urine [23]. The assessment of risk of bias is presented in table 1.

Analysis of the extracted data showed that there was clinical-, methodological and statistical heterogeneity among the included studies. The clinical heterogeneity consisted of diversity in outcomes, since outcomes were demonstrated as AUC_{0-4}, AUC_{0-6}, AUC_{0-8}, AUC_{0-12}, AUC_{0-24} and $AUC_{0\ -\ infinity}$. The methodological diversity consisted of heterogeneity regarding

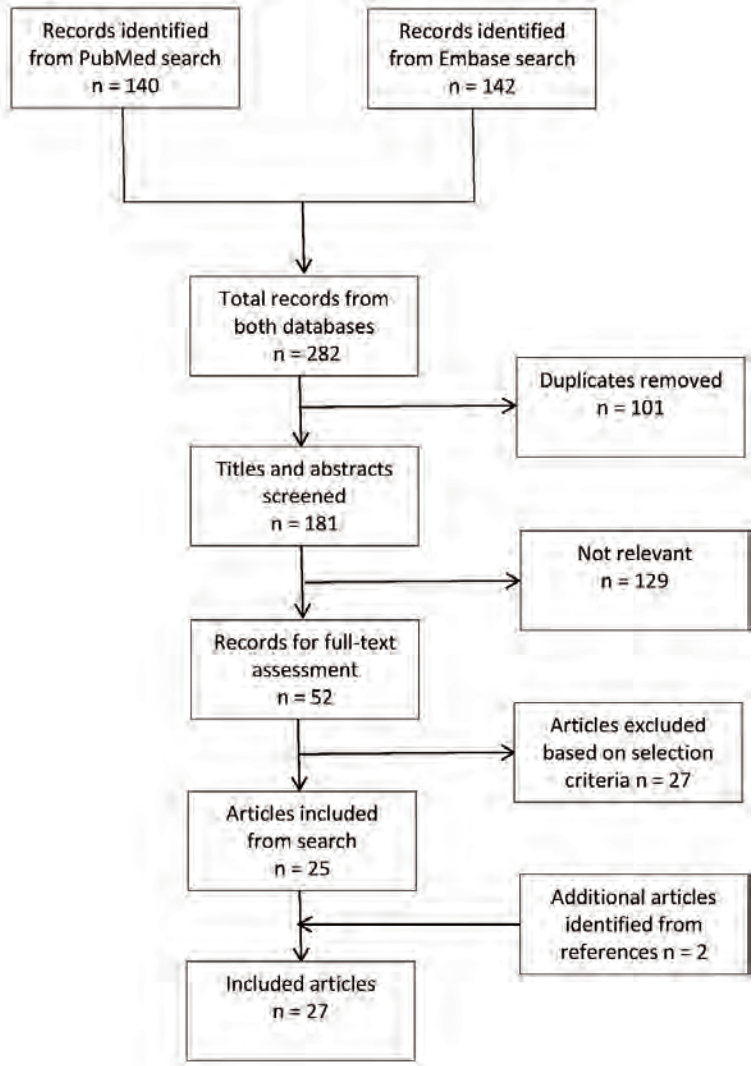

Figure 1. Flow chart of search and selection process

sampling time-points, number of samples collected, calculated AUC range, PK calculation methods and presentation of the results. As a result of the clinical- and methodological heterogeneity the data also showed high statistical heterogeneity as the main outcomes were inconsistent. As a result of the diversity the data were too heterogeneous to allow pooling. The pharmacokinetic variability within studies and between studies was high for all four drugs when comparing the mean or median AUC and C_{max}. The majority of the studies presenting PK data reported AUC (16 of 27 studies) and C_{max} (21 of 27 studies). One study reported data on V_d [32], 2 on CL [32,46], 8 on T_{max} [22,26,32,33,36,37,47,53] and 6 on $t_{1/2}$ [22,33,36,37,39,45].

Rifampicin

In total 21 of the included articles assessed the effect of HIV infection on RIF PK. A narrative synthesis of the results is presented in Table 2. Three articles reported a statistically significantly reduced RIF AUC for the HIV-positive TB group compared to the HIV-negative TB group [22,32,49]. One article found that the HIV group had a statistically significantly lower RIF AUC value compared to healthy HIV uninfected volunteers [33]. Another found the RIF AUC statistically significantly higher in the HIV-positive TB group than in the HIV negative TB group [26]. Five articles reported a statistically significant reduction of C_{max} in the HIV-positive TB group compared to the HIV-negative TB group [22,32,43,49,52] and one study showed a statistically significantly lower RIF C_{max} for the HIV group compared to healthy HIV uninfected volunteers [33]. One study demonstrated that excretion of RIF was reduced by 27% and 34% in the HIV-positive group with diarrhoea and HIV-TB co-infected group without diarrhoea respectively compared to the HIV uninfected TB group [23]. None of the included articles reported a statistically significant difference in T_{max} between HIV- negative and HIV-positive TB groups. Histograms from studies comparing HIV negative and HIV positive TB groups are plotted in figure 2A for the AUC and figure 3A for the C_{max}.

Isoniazid

Twenty included articles assessed the effect of HIV on INH PK (Table 2). None showed statistically significant differences in AUC between HIV negative and HIV positive TB groups. Two studies, both conducted in India, reported a statistically significant lower C_{max} in the HIV-positive TB group compared to the HIV-negative TB group [22,49]. One study showed a shorter T_{max} for the HIV-positive TB group compared to the HIV-negative TB group [32]. In the one study that measured excretion of INH, a significant reduction of the excretion by 24% was found in the HIV-positive group with diarrhoea and by 23% in the HIV-positive TB group without diarrhoea compared to the HIV uninfected TB group [23]. Histograms from studies comparing HIV negative and HIV positive TB groups are plotted in figure 2B for the AUC and figure 3B for the C_{max}.

Pyrazinamide

Seventeen included articles assessed the effect of HIV on PZA PK (Table 2). Two articles found that the HIV-positive TB group had statistically significantly reduced AUC compared to the HIV-negative TB group [32,45]. One article reported a statistically significant reduction of C_{max} in the HIV-positive TB group compared to the HIV-negative TB group [52]. Another study showed a statistically significantly shorter T_{max} for the HIV-positive TB group compared to the HIV-negative TB group [32]. Histograms from studies comparing HIV negative and HIV positive TB groups are plotted in figure 2C for the AUC and figure 3C for the C_{max}.

Ethambutol

Twelve included articles assessed the effect of HIV on EMB PK (Table 2). Three articles, all conducted in a paediatric population, showed that the HIV-positive TB group had statistically significantly reduced AUC compared to the HIV-negative TB group [32,45,47]. Two of these articles also reported a statistically significant reduction of C_{max} in the HIV-positive TB group compared to the HIV-negative TB group [32,45]. One study showed a statistically significant increase in T_{max} for the HIV-positive TB group compared to the HIV-negative TB group [47]. Histograms from studies comparing HIV negative and –positive TB groups are plotted in figure 2D for the AUC and figure 3D for the C_{max}.

Paediatrics

Seven studies were conducted in paediatric populations [32,38,42,45,47,49,51]. One lacked a comparator TB group [38], but compared their data with the reference ranges by Al Sultan et al. [54]. They concluded that C_{max} of RIF, INH and PZA were sub-therapeutic in 97%, 28% and 33% of the children, respectively. Of the remaining 6 paediatric studies, 4 reported that HIV co-infection in children with TB adversely affects the AUC and/or C_{max} for at least one of the FLDs [32,45,47,49] and 2 studies did not detect statistically significant differences between the groups [42,51].

Clinical relevance

The ratio in AUC between HIV-positive and HIV-negative TB groups is shown in figure 4. Three of the four studies reporting a statistically significantly reduced RIF AUC for the HIV-positive TB group compared to the HIV-negative TB group were clinically relevantly (≤ 80%) reduced [22,24,49], the fourth one was not considered clinically relevantly reduced [32]. The decrease in RIF AUC reported in HIV-positive patients without TB compared to healthy volunteers [33] was considered clinically relevant. The one study reporting a statistically significant increase of RIF AUC in the HIV-positive TB group compared to the HIV-negative TB group [26], was also considered clinically relevant (≥ 125%). Two studies demonstrated a statistically significantly reduced PZA AUC in the HIV-positive TB group compared to the HIV-negative TB group. One of them was considered borderline clinically relevant [45] and the other was not considered clinically relevant [32]. The results of all four studies showing a statistically significantly reduced EMB AUC in the HIV-positive TB group compared to the HIV-negative TB group were considered to be clinically relevant [24,32,45,47].

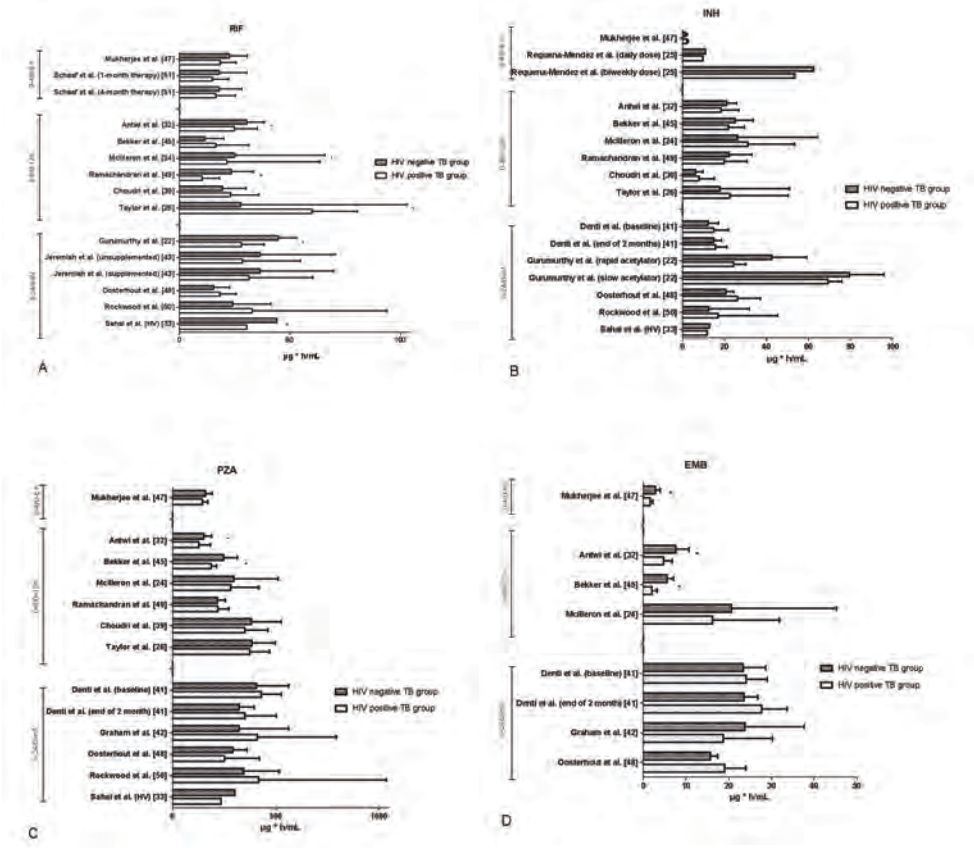

Figure 2. Histograms of the mean or median area under the concentration-time curve for the HIV negative TB group and the HIV positive TB group per study for [A] rifampicin, [B] isoniazid, [C] pyrazinamide and [D] ethambutol. *: statistical significance; 0-24/0-inf: AUC(0 – 24) and AUC(0 – infinity); 0-8/0-12: AUC(0 – 8) and AUC(0 – 12); 0-4/0-6; AUC(0 – 4) and AUC(0 – 6); the study of Sahai et al. [33] compared HIV infected individuals without TB with healthy HIV uninfected volunteers (HV).

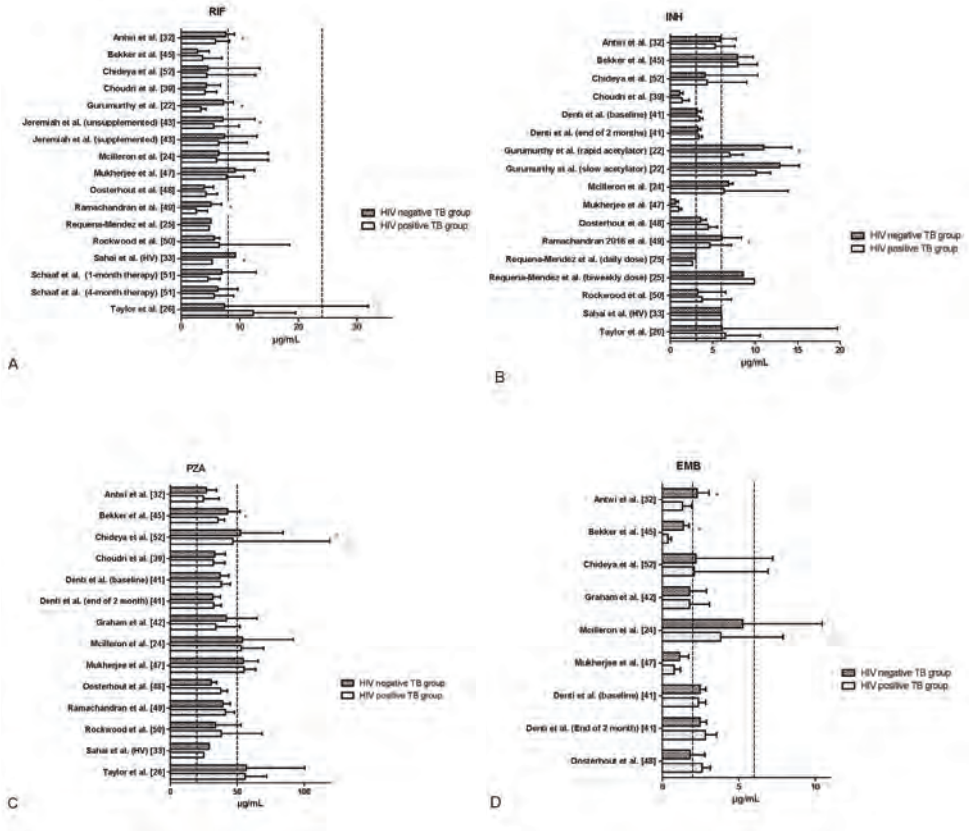

Figure 3. Histograms of the mean or median peak drug concentration for the HIV negative TB group and the HIV positive TB group per study for [A] rifampicin, [B] isoniazid, [C] pyrazinamide and [D] ethambutol. *: statistical significance, the dotted lines represent the generally cited reference ranges by Peloquin et al. [27] rifampicine 8 – 24 µg/mL; isoniazid 3 – 6 µg/mL; pyrazinamide 20 – 50 µg/mL; ethambutol 2 – 6 µg/mL; the study of Sahai et al. [33] compared HIV infected individuals without TB with healthy HIV uninfected volunteers (HV).

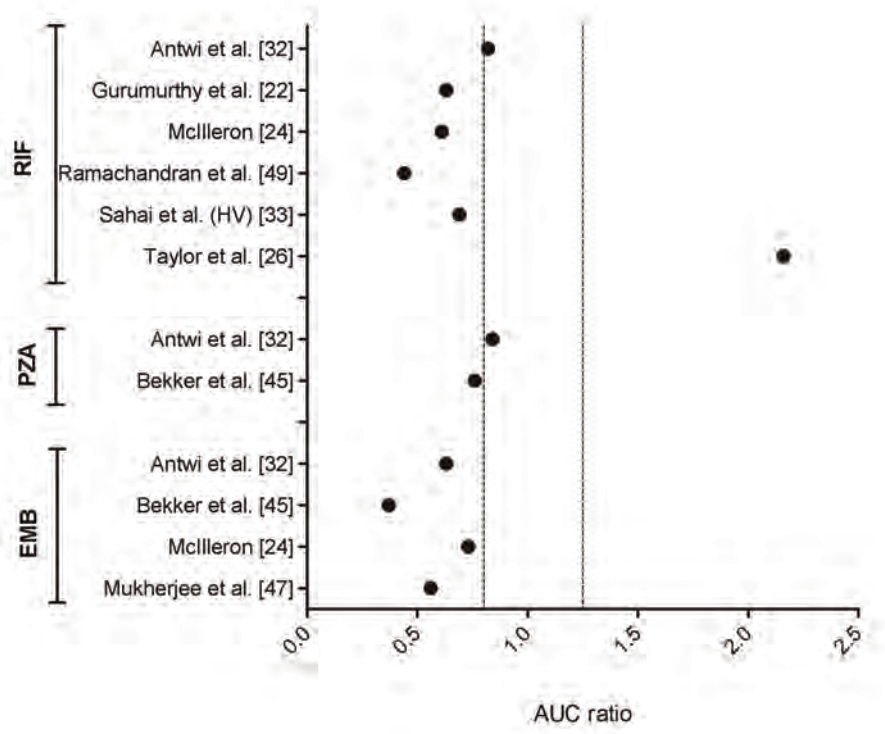

Figure 4. Ratio between area under concentration-time curves (AUC) of HIV-positive- and HIV-negative TB patients for studies showing statistically significant alteration in first-line TB drug AUCs stratified per drug. The dotted lines represent the 80%-125% (0.8 – 1.25) cut-off values for clinical relevance; all studies with a ratio outside this range were considered clinically relevant.

Discussion

To our knowledge this is the first systematic review investigating the effect of HIV infection on the PK of FLD. We found that the published data were heterogeneous and no consistent results emerged from our literature review. We also found that for EMB and in particular for RIF both HIV-positive and HIV-negative TB groups often did not achieve the generally accepted threshold (or minimally acceptable) C_{max} reference range of 8 µg/mL for RIF and 2 µg/mL for EMB [27]. This phenomenon was already observed in earlier studies and currently research is being conducted investigating higher dosages of RIF [55,56]. Although many studies showed a trend for lower AUC and/or C_{max} for at least one FLD in the HIV-positive TB group compared to the HIV-negative TB group, this did not always reach statistical significance. More than the half of the studies (11 out of 20) which included both HIV-positive and HIV-negative TB groups showed statistically significant different AUC and/or C_{max} for at least one FLD [22,24,26,32,33,43,45,47-49,52]. We focused on AUC and/or C_{max} since most of the studies reported these as primary endpoints and they are the most relevant PK predictors of clinical outcomes, especially when combined with data on MIC [9,11-13]. The majority of the articles focused on the PK of RIF and INH, which is justified by the fact that RIF and INH together are the backbone of drug-susceptible TB treatment.

The effect of HIV infection in TB patients, on the PK of TB FLDs is an on-going debate due to lack of consistent study results [54]. There may be several reasons to explain this inconsistency. First, several studies lacked a comparator group, making it difficult to adequately investigate the effect of HIV infection on the PK of the FLDs [34-38]. Instead, these studies compared with the widely cited reference ranges published by Peloquin et al. [27,57] and Alsultan et al. [54,58]. These reference ranges however are not age-, sex-, and weight matched and often racial and regional differences are not taken into account. Studies have shown that female sex is a determinant of higher RIF, INH and PZA concentrations and lower EMB concentration [18,24] and older age is a determinant of higher drug levels of all four FLDs [24,58]. Another study reported that RIF exposure was significantly lower in people of African descent when adjusted for dose and genetic polymorphisms [59]. Although comparing PK data with published reference ranges provides a basic impression, patient characteristics differ highly between different populations and conclusions from studies that compare PK finding with published reference ranges should therefore be regarded with caution.

Second, we postulate that the effect of HIV infection on the PK of the FLDs might often not have been detected due to a lack of power. Eleven of the studies which included both HIV-positive- and HIV-negative TB groups showed statistically significantly that HIV infection adversely affects the PK (mainly AUC and/or C_{max}) of at least one of the FLDs [22-24,32,33,43-45,47-49,52]. Eight studies with both groups included did not detect a statistically significant difference between the two groups for all four FLDs [19,25,39-42,46,51] and one study even demonstrated a

statistically significantly higher RIF AUC for the HIV positive TB group [26]. Studies showing statistical differences in drug exposures to any of the FLDs had higher sample sizes and therefore more power compared to the studies that failed to detect such differences.

The third potential contributor to the conflicting results published might be due to inadequate PK sampling and different PK calculation methods used. Studies unable to detect significant differences often had a lower number of collected blood samples for determination of drug concentrations. In addition to the varying numbers of collected blood samples, various different methods for AUC and C_{max} estimation were used. Some studies determined C_{max} by choosing the highest concentration among two or three blood draws [19,25,36,37]. A more reliable method for estimation of C_{max} is fitting a population PK curve to the measured serum concentration-time data using Bayesian estimation [60]. Due to the varying number of blood samples drawn over a certain period of time and the different methods used (model-based or non-compartmental) for the estimation of the AUC, the curves used to estimate AUCs in the included studies varied from 0 – 4 hours [47] to 0 – 24 hours [48,50] and thereby leading to potential loss of information. Collecting multiple blood samples over a longer period of time ensures adequately capturing the absorption, distribution, metabolism and elimination phases post-dose which results in more accurate estimations of the AUC. Another approach is limited sampling strategies (LSS) or computational posteriori estimations using Bayesian methods [60-62]. In this systematic review we therefore used the combination of the number of blood samples drawn, the use of PK modelling and the implementation of validated bio-analytical methods for the assessment of risk of bias.

Another explanation for the contrasting results in the included studies is variation in the clinical severity of HIV infection, the degree of immunosuppression and the use of ART. Several studies have demonstrated that the PK of the FLDs is more adversely altered in case of more advanced stages of HIV [22,33,52]. In the studies that did not find lower drug exposures among HIV-positive TB patients compared to the HIV-negative TB group, the majority of the co-infected patients had higher CD4+ cell counts and were on ART [41,45,48,50] or data on HIV progression was lacking [24,42]. It is conceivable that successful ART mitigates the effect of HIV infection on TB drug PK parameters. In 10 studies a proportion of the included HIV-positive participants was on ART [19,34,38,45-51] and 5 studies did not provide information on ART usage among HIV-positive TB patients [25,35-37,52]. The simultaneous usage of FLD and ART can result in drug-drug interactions [63,64] and potentially lead to non-adherence.

Among the included studies a high inter-individual PK variability was found which was not merely attributable to HIV infection. We found that in the majority of studies both HIV-positive and HIV-negative TB patients had a RIF C_{max} below the minimum reference range and the same applied for a proportion of the studies reporting EMB C_{max}. This high variability involves the interplay of multiple factors ranging from drug compounding to the distribution

of the drug molecules at the site of infection. Drug formulation [24], pharmacogenomics [20,21], racial- and ethnical differences [20,59], sex [19,24], body weight [18], advanced immunosuppression [22,33], co-morbid conditions such as diabetes mellitus [19,23], co-medication [63,64] and nutritional status [43,65] are the most investigated and salient factors. It is worth mentioning that a statistically significant reduction of FLD exposure in the HIV-positive TB groups does not necessarily have to be clinically relevant and that this has to be explored in future studies that include treatment outcomes. In the absence of such studies at present, the cut-off values of EMA guidelines (< 80% and > 125%) [29,30] offer an alternative way to determine the clinical relevance of decreased or increased FLD exposures. Since these cut-off values are based on drug exposure, only studies reporting a statistically significant change in AUC could be included in the assessment. With the exception of the studies by Antwi et al. [32] and Taylor et al. [26] for RIF and Antwi et al. [32] for PZA AUC, all studies reporting a statistically significant alteration in FLD AUC were considered clinically relevantly reduced [22,24,26,32,33,45,47,49]. Taking the risk of bias assessment (table 1) into account in relation to the studies included in the systematic review, we postulate that in patients prone to low FLD exposure, HIV infection might even further reduce drug exposure [66], leading to poor treatment outcome [9]. Therapeutic drug monitoring (TDM), while not a substitute for clinical judgement, could be a powerful tool for identifying patients with sub-therapeutic FLD levels at risk of poor treatment outcomes [62,67,68]. TDM performed early during TB treatment in patients at risk of sub-therapeutic FLD levels may improve treatment response and may also prevent toxicity [68,69]. For resource-limited settings Dried Blood Spot analysis combined with limited sampling strategies (LSS) or drug concentration measurements in saliva with thin-layer chromatography might provide a solution to address problems of patients with the burden of blood draws as well as costs [61,70,71].

A recent study by Hiruy et al. reported that HIV-negative children with TB are at risk of sub-therapeutic concentrations for all FLDs [72]. Younger age has a considerable impact on TB drug exposure and should be considered in dosing recommendations. This has been attributed to children having a larger liver size and higher hepatic metabolic activity in proportion to body weight [53]. Our findings suggest that RIF and EMB exposures appear to be adversely affected in paediatric HIV-positive TB populations, even after administration of the revised World Health Organisation (WHO) recommended weight-based dosages. The clinical relevance of such reduced FLD exposures has to be further investigated urgently in paediatric populations.

A broad and comprehensive literature search was conducted systematically that allowed the identification of studies with data on the effect of HIV infection on the PK of the FLDs. A strength of this systematic review is that it provides a good overview of the available literature and exposes current knowledge gaps. The systematic review also has some limitations. Despite the high disease burden, relatively few data were available and with

variable quality, increasing the risk of bias. In this systematic review we chose to include all articles with data on the effect of HIV infection on the PK of the FLDs to prevent loss of information and therefore studies lacking a comparator group and with participants on ART were included, potentially introducing bias. A more in-depth analysis was restricted to studies that had both an HIV-positive and an HIV-negative TB group. Although no registered and unpublished studies were found in the database search, publication bias cannot completely be excluded. A recent study demonstrated that higher MIC values were associated with a greater risk of relapse than lower MIC values [73]. None of the studies included in this systematic review reported data on MIC. Lastly, the published data were too heterogeneous and reported highly inconsistently, to allow pooling of the data. Due to methodological and statistical heterogeneity subgroup analyses were also not appropriate.

Conclusion

In conclusion, relatively few studies have been published investigating the effect of HIV infection on the PK of the FLD. The available studies provide a heterogeneous dataset from which consistent results could not be obtained. Therefore, we could make no general recommendation with respect of dosing. There is a need for a consistent and homogeneous approach to studies and for a uniform quality assessment tool specifically for PK studies. Taking clinical relevance into account, we postulate that HIV infection may exacerbate a susceptibility to low FLD exposures, with potential detrimental consequences for treatment outcomes. This systematic review may inform further studies investigating the effect of HIV infection on the PK of the FLDs. A population PK analysis may provide a solution for the inability of pooling of the currently available data as a population PK analysis can adjust for confounders. In addition, a prospective study with both an HIV-positive- and HIV-negative TB group including data on pharmacodynamics and treatment outcome is needed to provide further insight in the highly complex PK of the FLDs.

Table 1. Overview of studies investigating the effect of HIV infection on the AUC and C_{max} of rifampicin, isoniazid, pyrazinamide and ethambutol.

RIFAMPICIN

Authors	Country	Study period	Age group	Comparator (n)	HIV positive group (n)	Effect on AUC	Effect on C_{max}	Additional PK data
Antwi et al. [32]	Ghana	2012-2015	Ped	TB (54)	HT (59)	AUC(0-8) decreased 18,3%*	C_{max} decreased 23,8%*	
Bekker et al. [45]	South Africa	2014-2015	Ped	TB (34)	HT (5)	AUC(0-8)↔#	↔#	
Chideya et al. [52]	Botswana	1997-2000	Adult	TB (70)	HT low CD4+ (84) HT high CD4+ (71)	_	↔ for HT group with low CD4+, C_{max} increased 24%* for HT group with high CD4+	
Choudri et al. [39]	Kenya	1994-1995	Adult	TB (15)	HT (14)	AUC (0-12)↔#	↔#	
Conte et al. [46]	United States	_	Adult	HV (20)	HIV (20)	_	_	HIV status had no effect on C_2 and C_4 plasma concentrations
Gurumurthy et al. [22]	India	2002	Adult	TB (13)	HIV (13) HT (15)	AUC (0-inf) decreased 52,5%* for HIV group with low CD4+, AUC(0-inf) decreased 36,8%* for HT group#	C_{max} decreased 52,8%* for both groups#	
Gurumurthy et al. [23]	India	2001	Adult	TB (23)	HIV (40) HT (26)	_	_	Excretion was reduced 27%* and 34%* for HIV and HT group respectively#
Jaruratanasirikul et al. [35]	Thailand	_	Adult	None	HT (8)	_	_	Mean C_{max} was 9,81 ± 4,41 µg/mL and mean AUC(0-24) was 60,25 ± 36,88 µg.h/mL#
Jeremiah et al. (unsupplemented) [43]	Tanzania	2010-2011	Adult	TB (25)	HT (24)	AUC(0-24)↔	C_{max} decreased 21,8%*	
Jeremiah et al. (supplemented) [43]	Tanzania	2010-2011	Adult	TB (25)	HT (26)	AUC(0-24)↔	↔	
Mcilleron et al. [24]	South Africa	1999-2002	Adult	TB (127)	HT (14)	AUC(0-8) decreased 39%*	_	
Mukherjee et al. [47]	India	2009-2013	Ped	TB (32)	HT (24)	AUC(0-4)↔#	↔#	
Oosterhout et al. [48]	Malawi	2007-2008	Adult	TB (17)	HT (30)	↔#	↔#	HIV did not affect PK parameters
Peloquin et al. [34]	United States	1993-1994	Adult	TB (lit)	HT (26)	_	_	2-hour serum concentrations were measured.
Perlman et al. (daily dose) [37]	United States	_	Adult	TB (lit)	HT (34)	_	_	76% of recipients had lower C_{max} values compared to published range (<8 µg/mL)

Table 1. Continued

Perlman et al. (intermittent dose) [37]	United States	_	Adult	TB (lit)	HT (21)	_	_	68% of recipients had lower C_{max} values compared to published range (<8 µg/mL)
Ramachandran et al. [38]	India	2010-2013	Ped	TB (lit)	HT (77)	_	_	97% of recipients had lower C_{max} values compared to published range (<8 µg/mL)
Ramachandran et al. [49]	India	2010-2013	Ped	TB (84)	HT (77)	AUC(0-8) decreased 55,6% *	C_{max} decreased 49,0%*	
Requena-Mendez et al. [19]	Peru	2009	Adult	TB (50)	HT (29)	_	_	Plasma C_2 and C_6 ↔
Rockwood et al. [50]	South Africa	2013-2014	Adult	TB (35)	HT (65)	AUC(0-24)↔	↔	HIV was associated with a 21%* decrease in clearance
Sahai et al. [33]	Canada	_	Adult	HV (12)	HIV low CD4+ (24) HIV high CD4+ (12)	AUC(0-24) decreased 30,8% for HIV group with low CD4+*, AUC(0-24) decreased 28,8%* for HIV group with high CD4+#	C_{max} decreased 42,9%* for HIV group with low CD4+, C_{max} decreased 36,3%* for HIV group with high CD4+#	
Schaaf et al. (1-month therapy) [51]	South Africa	2004-2006	Ped	TB (33)	HT (21)	AUC(0-6)↔#	↔#	
Schaaf et al. (4-month therapy) [51]	South Africa	2004-2006	Ped	TB (33)	HT (21)	AUC(0-6)↔#	↔#	
Taylor et al. [26]	South Africa	1998	Adult	TB (14)	HT (13)	AUC (0-12) increased 216%*	↔	

ISONIAZID

First author	Country	Study period	Age group	Comparator (n)	HIV positive group (n))	Effect on AUC	Effect on Cmax	Additional PK data
Antwi et al. [32]	Ghana	2012-2015	Ped	TB (54)	HT (59)	AUC(0-8)↔	↔	
Bekker et al. [45]	South Africa	2014-2015	Ped	TB (34)	HT (5)	AUC(0-8)↔#	↔#	
Chideya et al. [52]	Botswana	1997-2000	Adult	TB (70)	HT low CD4+ (84) HT high CD4+ (71)	_	↔ for both groups	
Choudri et al. [39]	Kenya	1994-1995	Adult	TB (15)	HT (14)	AUC(0-12)↔#	_	
Conte et al. [40]	United States	_	Adult	HV (40)	HIV low CD4+ (4) HIV high CD4+ (36)	_	_	HIV status had no effect on C_1 and C_4 plasma concentrations
Denti et al. [41]	Tanzania	2010-2011	Adult	TB (50)	HT (50)	AUC (0-24) ↔	↔	
Gurumurthy et al. (rapid acetylator) [22]	India	2002	Adult	TB (5)	HIV (9) HT (8)	AUC (0-inf) ↔ for both groups#	↔ for HIV group, C_{max} decreased 36,4%* for HT group#	

Table 1. Continued

Gurumurthy et al. (slow acetylator) [22]	India	2002	Adult	TB (8)	HIV (4) HT (7)	AUC (0-inf) ↔ for both groups#	↔ for both groups#	
Gurumurthy et al. [23]	India	2001	Adult	TB (23)	HIV (40) HT (26)	_	_	Excretion was reduced 24%* and 23%* for HIV and HT group respectively#
Mcilleron et al. [24]	South Africa	1999-2002	Adult	TB (127)	HT (14)	AUC(0-8) ↔	_	
Mukherjee et al. [47]	India	2009-2013	Ped	TB (32)	HT (24)	AUC(0-4)↔#	↔#	
Oosterhout et al. [48]	Malawi	2007-2008	Adult	TB (17)	HT (30)	↔#	↔#	HIV did not affect PK parameters
Peloquin et al. [34]	United States	1993-1994	Adult	TB (lit)	HT (26)	_	_	2-hour serum concentrations were measured.
Ramachandran et al. [38]	India	2010-2013	Ped	TB (lit)	HT (77)	_	_	28% of recipients had lower C_{max} values compared to published range (<3 µg/mL)
Ramachandran et al. [49]	India	2010-2013	Ped	TB (84)	HT (77)	AUC(0-8)↔	C_{max} decreased 23,0%*	
Requena-Mendez et al. (daily dose) [25]	Peru	2009	Adult	TB (32)	HT (16)	AUC(0-6)↔#	↔#	
Requena-Mendez et al. (biweekly dose) [25]	Peru	2009	Adult	TB (18)	HT (13)	AUC(0-6)↔#	↔#	
Rockwood et al. [50]	South Africa	2013-2014	Adult	TB (35)	HT (65)	AUC(0-24)↔	↔	HIV was associated with a 23%* decrease of clearance
Sahai et al. [33]	Canada	_	Adult	HV (12)	HT low CD4+ (24) HT high CD4+ (12)	AUC (0-24) ↔ for both groups#	↔ for both groups#	
Taylor et al. [26]	South Africa	1998	Adult	TB (14)	HT (13)	AUC(0-12)↔	↔	

PYRAZINAMIDE

First author	Country	Study period	Age group	Comparator (n)	HIV positive group (n)	Effect on AUC	Effect on Cmax	Additional PK data
Antwi et al. [32]	Ghana	2012-2015	Ped	TB (54)	HT (59)	AUC(0-8) decreased 16,2%*	↔	
Bekker et al. [45]	South Africa	2014-2015	Ped	TB (34)	HT (5)	AUC(0-8) decreased 21%*,#	C_{max} decreased 15%*,#	
Chideya et al. [52]	Botswana	1997-2000	Adult	TB (70)	HT low CD4+ (84) HT high CD4+ (71)	_	C_{max} decreased 10,3%* for HT with low CD4+ group, ↔ for HT with high CD4+ group	

Table 1. Continued

Choudri et al. [39]	Kenya	1994-1995	Adult	TB (15)	HT (14)	AUC(0-12)↔#	↔#	
Denti et al. [41]	Tanzania	2010-2011	Adult	TB (50)	HIV low CD4+ (4) HIV high CD4+ (36)	AUC (0-24) ↔	↔	
Graham et al. [42]	Malawi	2000-2001	Ped	TB (9)	HT (18)	AUC (0-24)↔#	↔#	
Gurumurthy et al. [22]	India	2002	Adult	TB (13)	HIV (13) HT (15)	_	_	Dosage excreted in urine was reduced 35%* and 48%* for HIV and HT group respectively#
Mcilleron et al. [24]	South Africa	1999-2002	Adult	TB (127)	HT (14)	↔	↔	
Mukherjee et al. [47]	India	2009-2013	Ped	TB (32)	HT (24)	AUC(0-4)↔#	↔#	
Oosterhout et al. [48]	Malawi	2007-2008	Adult	TB (17)	HT (30)	↔#	C_{max} decreased 15%*,#	
Peloquin et al. [34]	United States	1993-1994	Adult	TB (lit)	HT (26)	–	–	2-hour serum concentrations were measured.
Perlman et al. (daily dose) [36]	United States	_	Adult	TB (lit)	HT (24)	–	–	6,4% of recipients had lower C_{max} values compared to published range (<20 µg/mL)
Perlman et al. (intermittent dose) [36]	United States	_	Adult	TB (lit)	HT (23)	–	–	4,0% of recipients had lower C_{max} values compared to published range (<25 µg/mL)
Ramachandran et al. [38]	India	2010-2013	Ped	TB (lit)	HT (77)	–	–	33% of recipients had lower C_{max} values compared to published range (<35 µg/mL)
Ramachandran et al. [49]	India	2010-2013	Ped	TB (84)	HT (77)	AUC(0-8)↔	↔	
Rockwood et al. [50]	South Africa	2013-2014	Adult	TB (35)	HT (65)	AUC(0-24)↔	↔	
Sahai et al. [33]	Canada	_	Adult	HV (12)	HT low CD4+ (24) HT high CD4+ (12)	AUC(0-24)↔ for both groups#	↔#	
Taylor et al. [26]	South Africa	1998	Adult	TB (14)	HT (13)	AUC(0-12)↔	↔	

ETHAMBUTOL

First author	Country	Study period	Age group	Comparator (n)	HIV positive group (n)	Effect on AUC	Effect on C_{max}	Additional PK data
Antwi et al. [32]	Ghana	2012-2015	Ped	TB (54)	HT (59)	AUC(0-8) decreased 37,1%*	C_{max} decreased 41,7%*	
Bekker et al. [45]	South Africa	2014-2015	Ped	TB (14)	HT (2)	AUC(0-8) decreased 63,0%*#	C_{max} decreased 71,7%*,#	

Table 1. Continued

Chideya et al. [52]	Botswana	1997-2000	Adult	TB (70)	HT low CD4+ (84) HT high CD4+ (71)	_	C_{max} ↔ for both groups	
Denti et al. [41]	Tanzania	2010-2011	Adult	TB (50)	HT (14)	AUC (0-24) ↔	↔	
Graham et al. [42]	Malawi	2000-2001	Ped	TB (12)	HT (6)	_	↔	
Gurumurthy et al. [22]	India	2002	Adult	TB (13)	HIV (13) HT (15)	_	_	Dosage excreted in urine was reduced 43%* and 19%* for HIV and HT group respectively#
Jönsson et al. [44]	South Africa	_	Adult	TB (165)	HT (24)	_	_	HIV was associated with 15% decrease of bioavailability
Mcilleron et al. [24]	South Africa	1999-2002	Adult	TB (127)	HT (14)	AUC(0-8) decreased 27%*	↔	
Mukherjee et al. [47]	India	2009-2013	Ped	TB (32)	HT (24)	AUC(0-4) decreased 44,4%*,#	↔#	
Oosterhout et al. [48]	Malawi	2007-2008	Adult	TB (17)	HT (30)	↔#	↔#	
Peloquin et al. [34]	United States	1993-1994	Adult	TB (lit)	HT (26)	_	_	2-hour serum concentrations were measured.
Perlman et al. (daily dose) [37]	United States	_	Adult	TB (lit)	HT (48)	_	_	69% of recipients had lower C_{max} values compared to published range (<2 µg/mL)
Perlman et al. (intermittent dose) [37]	Unites States	_	Adult	TB (lit)	HT (20)	_	_	39% of recipients had lower Cmax values compared to published range (<4 µg/mL)

Age group: paediatric or adult, n: number of participants, TB: participants with only tuberculosis, HT: TB/HIV co-infected participants, HV: healthy volunteers, AUC: area under the concentration-time curve, C_{max}: peak drug concentration , PK: pharmacokinetic, low CD4+ = <200 cells/µL, high CD4+ = ≥200 cells/µL, ↔: no statistical significant difference, (-): no information, *:statistically significant, all the PK data are expressed as median except for # which represents mean

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Appendix I

Authors	Participants					Study Design					Bioanalytical		Endpoints/follow-up						Grading[a]
	Both HIV+ and HIV- TB groups included	Total number of participants	HIV and TB confirmation tests described	Number of participants CD4 <200 cells/µL or CD4%<12	Proportion of HIV positive participants on ART	Absorption test conducted	PK altering comorbidities taken into account	Interacting (non-ART) co-medication described	Given dosage in mg/kg known per group	DOT	Validated analytical determination	Specimen handling described	Number of plasma samples	Method of AUC calculation	AUC calculation	C_{max} calculation	AUC and C_{max} data stratified per arm	Number of participants lost to follow-up or died	Risk of bias (high, medium or low)
Antwi et al. [32]	+	113	+	+/-	0/59	-	-	-	+	+	+	+	5	Noncompartmental	+/-	+	+	6	Medium
Bekker et al. [45]	+	39	+/-	0	5/5	-	-	-	+	+	+	+	6	Noncompartmental	+/-	+	+	2	Medium
Chideya et al. [52]	+	225	+	84	-	-	-	-	-	+	+	+	3	Noncompartmental	-	-	+/-	17	High
Choudri et al. [39]	+	29	+/-	8	0/14	+	+	+	-	+	+	+	9	Noncompartmental	+	+	+	-	Low
Conte et al. [40]	+	80	+/-	+/-	0/40	-	+	+	-	+/-	+	+	2	n.a.	n.a.	-	-	0	High
Conte et al. [46]	+	40	+/-	-	10/20	-	+	+	-	+/-	+	+	3	n.a.	n.a.	-	-	-	High
Denti et al. [41]	+	100	+	+/-	0/50	-	-	-	-	+	+	+	3	Model based	+	+	-	8	Medium
Graham et al. [42]	+	45	+	-	0/18	-	+/-	-	+	+	+	+	7	Noncompartmental	+	+	+/-	-	Medium
Gurumurthy et al. [22]	+	41	+/-	+/-	0/28	-	-	-	+	+	+	-	5	Noncompartmental	+	+	+	-	Medium
Gurumurthy et al. [23]	+	99	+	+/-	0/66	+	+	+	-	+	+	+	0	n.a.	n.a.	n.a.	n.a.	-	Medium

Appendix I. Continued

Jaruratanasirikul et al. [35]	-	8	+/-	0	-	-	+	-	-	-	-	+/-	14	Noncompartmental	+	+	-	-	High
Jeremiah et al. [43]	+	100	+	+/-	0/50	-	-	-	-	+	+	+	3	Model based	+	+	+	8	Medium
Jönsson et al. [44]	+	189	-	-	0/24	-	-	-	-	+	+	+	10	Model based	-	-	-	0	High
Mcilleron et al. [24]	+	142	-	-	0/9	-	-	+	+	+	+	+	10	Model based	+	+	+	-	Medium
Mukherjee et al. [47]	+	56	+	+/-	19/24	-	+	-	+	+	+	+	4	Noncompartmental	-	+	+	-	Medium
Oosterhout van et al. [48]	+	47	+	+/-	14/30	-	+/-	-	-	-	+	+	9	Model based	+	+	+	-	Medium
Peloquin et al. [34]	-	26	+	23	4/26	-	+	+	+	+	+/-	+	1	n.a.	n.a.	n.a.	n.a.	0	High
Perlman et al. [36]	-	48	+	36	-	-	+	+	+	+	+	+	3	Noncompartmental	-	+	n.a.	5	Medium
Perlman et al. [37]	-	59	+	39	-	-	+	+	+	+	+	+	3	Model based	-	+	n.a.	5	Medium
Ramachandran et al. [38]	-	77	+	+/-	45/77	-	-	-	+	+	+	+	5	Noncompartmental	+/-	+	n.a.	5	Medium
Ramachandran et al. [49]	+	161	+	+/-	45/77	-	-	-	+	+	+	+	5	Noncompartmental	+/-	+	+	-	Medium
Requena-Mendez et al. [19]	+	79	-	+/-	8/29	-	+	-	+	+	+	+	2	n.a.	-	+	+/-	29	Medium
Requena-Mendez et al. [25]	+	82	-	-	-	-	+	-	-	+	-	+	2	Noncompartmental	-	+	+	8	High
Rockwood et al. [50]	+	100	+	29	50/65	-	-	-	+	+	+	+	7	Model based	+	+	+	8	Low
Sahai et al. [33]	+	48	-	24	0/36	+	+	+	+	+	+	+	13	Model based	+	+	+	-	Low
Schaaf et al. [51]	+	60	+/-	-	2/21	-	-	-	-	+	+	+	5	Noncompartmental	+/-	+	+	6	Medium
Taylor et al. [26]	+	27	-	13	0/13	-	+	+	+	+	+	+	19	Noncompartmental	+	+	+	-	Low

(+): present, (-): absent or not provided, (+/-): partially/incomplete, n.a.: not applicable, ART: antiretroviral therapy, DOT: directly observed therapy

AUC calculation:

Model based and AUC > (0 – 8 hours) = +

Noncompartmental and AUC > (0 – 8 hours) and ≥ 5 plasma samples = +

Noncompartmental and AUC ≤ (0 – 8 hours) and ≥ 5 plasma samples = +/-

Noncompartmental and AUC > (0 – 8 hours) and < 5 plasma samples = +/-

Model based and AUC ≤ (0 – 8 hours) = +/-

Noncompartmental and AUC ≤ (0 – 8 hours) and < 5 plasma samples = -

[a]Grading: the grading of the studies was performed based on the risk of bias. 1 – 6 points: high risk of bias; 7 – 9 points: medium risk of bias; 10 – 12: low risk of bias. Note: in the absence of a validated risk of bias assessment of pharmacokinetic studies our strategy was based on the summary of strength and weaknesses of the included studies.